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The United Kingdom Diabetic Retinopathy Electronic Medical Record Users Group: Report 3: Baseline Retinopathy and Clinical Features Predict Progression of Diabetic Retinopathy

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Abstract

PURPOSE—To determine the time and risk factors for developing proliferative diabetic retinopathy (PDR) and vitreous hemorrhage (VH).

DESIGN—Multicenter, national cohort study.

METHODS—Anonymized data of 50 254 patient eyes with diabetes mellitus at 19 UK hospital eye services were extracted at the initial and follow-up visits between 2007 and 2014. Time to progression of PDR and VH were calculated with Cox regression after stratifying by baseline diabetic retinopathy (DR) severity and adjusting for age, sex, race, and starting visual acuity.

RESULTS—Progression to PDR in 5 years differed by baseline DR: no DR (2.2%), mild (13.0%), moderate (27.2%), severe nonproliferative diabetic retinopathy (NPDR) (45.5%). Similarly, 5-year progression to VH varied by baseline DR: no DR (1.1%), mild (2.9%), moderate (7.3%), severe NPDR (9.8%). Compared with no DR, the patient eyes that presented with mild, moderate, and severe NPDR were 6.71, 14.80, and 28.19 times more likely to develop PDR, respectively. In comparison to no DR, the eyes with mild, moderate, and severe NPDR were 2.56, 5.60, and 7.29 times more likely to develop VH, respectively. In severe NPDR, the eyes with intraretinal microvascular abnormalities (IRMA) had a significantly increased hazard ratio (HR) of developing PDR (HR 1.77, 95% confidence interval [CI] 1.25–2.49, P =.0013) compared with those with venous beading, whereas those with 4-quadrant dot-blot hemorrhages (4Q DBH) had 3.84 higher HR of developing VH (95% CI 1.39–10.62, P = .0095).

CONCLUSIONS—Baseline severities and features of initial DR are prognostic for PDR development. IRMA increases risk of PDR whereas 4Q DBH increases risk of VH.

Diabetic Retinopathy (DR) is the Leading cause of blindness in working-age adults worldwide.[1] More than 5 million were affected in 2005 and this number is projected to triple to 16 million by 2050 in the United States alone.[2] Even though early detection of DR can substantially decrease the risk of blindness, the nonadherence rate of DR screening has been reported as high as 69%.[3]

The progression to vision-threatening proliferative diabetic retinopathy (PDR) primarily depends on the stage of DR severity. The Early Treatment Diabetic Retinopathy Study (ETDRS) has revealed that the risk of progression from severe nonproliferative diabetic retinopathy (NPDR) to proliferative diabetic retinopathy (PDR) is approximately 52% in 1 year.[4] Since the time of ETDRS, the management of diabetes has changed significantly.[5] Thus, more recent clinical trials or epidemiologic studies have revealed varying rates of PDR progression from baseline DR in 4 years, ranging from 5.3 to 11.0%.[6–10]

The key classification of DR was originally defined in the Airlie House Symposium in 1968 and modified in several landmark trials to date.[11,12] In particular, the modified classification used in the ETDRS has been used widely in research settings but involved a complex scoring system ranging from 10 to 85 and required comparison with the standard photographs.[12] As a result, even more simplified, clinical classification systems are more commonly used nowadays.[13,14] However, whether more granular, feature-based criteria can predict PDR progression on a large scale has not been studied, to our knowledge. In addition, progression rates of retinopathy in the context of current systemic management have not been adequately

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explored with real-world data. This information will be important in guiding follow-up intervals on monitoring for diabetic retinopathy and advising the patients and their diabetic care team regarding progression risk, as well as in the powering of clinical trials for interventions that may prevent the progression of diabetic retinopathy.

The United Kingdom Diabetic Retinopathy Electronic Medical Record (UK DR EMR) Users Group database is unique in that each clinical feature of diabetic retinopathy is entered by physicians at baseline and at each retina clinic visit in a structured manner. The DR score is then generated automatically based on the ETDRS criteria by aggregating the recorded feature, thus providing us with an enriched clinical dataset to study the validity of clinical features in predicting DR progression. The purpose of our paper was to perform an EMR-based epidemiologic study to determine current rates of DR progression in the UK study cohort and define the time to progression to PDR and vitreous hemorrhage (VH), 2 important clinical endpoints of DR, in diabetic patients who present to eye care providers for the first time. In addition, we sought to determine the clinical features of diabetic retinopathy that are most predictive of progression to PDR.

METHODS

ETHICS APPROVAL

This study was conducted in accordance with the Declaration of Helsinki and the UK Data Protection Act. The lead clinician and Caldicott Guardian, who are responsible for protecting confidentiality of patient information, at each participating center gave written approval for extraction of anonymized data. The study protocol was approved by the head of research governance at the lead clinical center.

DATA EXTRACTION

Anonymized data were remotely extracted from 19 centers using the same EMR system (Medisoft Ophthalmology, Medisoft Limited, Leeds, UK) in November 2014. Each site is the only NHS provider of diabetic retinopathy care to their local population and very few patients switch between providers or access care privately. All patients were first-time presenters to eye providers after being referred from the UK national diabetic retinopathy screening program, a nationwide program implemented through the National Health Service (NHS) and maintained by rigorous quality assurance measures.[15] Patients who received anti–vascular endothelial growth factor (anti-VEGF) injections during the study period were excluded. Data were extracted through the EMR compulsory DR structured assessment module, as described previously.[16] Demographic data were extracted from the hospital's patient administration system to the EMR. All patients had data extracted from the time of their first DR structured assessment entry onto the EMR to the date of their last clinical entry before the data extraction on November 26, 2014.

ELECTRONIC MEDICAL RECORDS RECORDING OF CLINICAL VARIABLES

Physicians were asked to fill out the characteristics of retinopathy and maculopathy findings on drop-down menus. Each retina evaluation screen showed the standard ETDRS 8a[4] and 2a[4] photographs for intraretinal microvascular abnormalities (IRMA) and dot-blot

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hemorrhages (DBH), respectively. The following nonproliferative features were included: IRMA (choices of none, <8a in 1–4 quadrants, >8a in 1 quadrant, >8a in 2 quadrants, >8a in 3 quadrants, >8a in 4 quadrants), venous beading (none, 1 quadrant, 2 or more quadrants), venous loops/reduplication (yes or no), hemorrhages (none, microaneurysms [MA] only, hemorrhages < next level, ≥4 blot hemorrhages in any quadrant and ≥8 in total, ≥2a in any quadrant, >2a in all quadrants), cotton-wool spots (none, ≤5, >5). The fields that were required to define ETDRS grade were compulsory.

CLINICAL VARIABLES

Clinical features that were extracted include presence and extent of the following features: MA only, hemorrhages/MA < standard ETDRS photograph $2a^4$, ≥4 DBHs in any quadrants and ≥8 in total, DBHs > standard ETDRS photograph $2a^4$ in any quadrant, DBHs > standard ETDRS photograph $2a^4$ in all quadrants, IRMA ≥ standard ETDRS photograph $8a^4$ in 1 quadrant, venous beading, venous loops/replication, cotton-wool spots, and scars of prior photocoagulation. The composite ETDRS scores were automatically generated in the EMR.

STATISTICAL ANALYSES

Eyes with neovascularization at baseline were excluded from survival analyses. Kaplan-Meier survival curves were generated to demonstrate the rate of progression to PDR based on each clinical feature. Cox proportional hazards regression models were used with baseline age, sex, and presenting visual acuity (VA) as prognostic variables. The primary outcome was the time from the date of patients' first eye examination until the first time of the respective grade of retinopathy. If the eyes did not reach the respective retinopathy, they were censored at the time of their latest follow-up examination. Time to PDR or VH analyses were stratified by baseline diabetic retinopathy status. All analyses were performed at the patient-eye level, and analyses were repeated with random selection of 1 eye per patient to evaluate the intercorrelation. All statistics were performed using R version 3.2.5 (http://www.r-project.org).

RESULTS

A Total of 64 224 Eyes (33 698 Patients) were Identified with having at least 2 DR assessments and no neovascularization at baseline; 3970 eyes were excluded because of anti-VEGF injections. A total of 60 254 patient eyes (32 553 patients) were included in the study. The mean age was 64.89 (interquartile range [IQR] 55.10–76.68), and 63.97% were white. The overall mean presenting VA was 72.60 ETDRS letters (IQR 70.0–85.0) (Table 1). Diabetic retinopathy was present in 72.4% of diabetic patients at initial presentation to an eye care provider.

PROGRESSION TO PROLIFERATIVE DIABETIC RETINOPATHY BY DIABETIC RETINOPATHY SEVERITY

The percentages of progression to PDR by years 1, 3, and 5 per baseline DR were the following: no DR (0.3%, 1.0%, 2.2%, respectively), very mild (0.7%, 3.8%, 7.9%), mild (1.5%, 6.9%, 13.0%), moderate (4.0%, 16.1%, 27.2%), severe (9.6%, 31.6%, 45.5%), and very severe NPDR (24.7%, 55.8%, 67.7%) (Figure 1).

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The hazards of progressing to PDR in patient eyes that presented with very mild and mild NPDR compared with no DR were 4.02 (95% confidence interval [CI] 3.25–4.96) and 6.71 (95% CI 5.46–8.24), respectively, after adjusting for age, sex, race, and initial VA. Furthermore, in comparison to the patient eyes with no DR, the hazards of PDR progression in moderate, severe, and very severe NPDR were 14.8 (95% CI 12.1–18.1), 28.2 (95% CI 22.9–34.7), and 58.4 (95% CI 47.0–72.7), respectively, after adjusting for age, sex, race, and initial VA (Table 2).

PROGRESSION TO PROLIFERATIVE DIABETIC RETINOPATHY BY DIABETIC RETINOPATHY FEATURES

In subanalysis that included only patient eyes with severe NPDR (n = 2823), a total of 715 eyes with IRMA, 240 eyes with venous beading, and 169 eyes with 4-quadrant (4Q) DBH were found. In this group, the percentages of progression to PDR by years 1, 3, and 5 were highest in patient eyes with IRMA (10.5%, 31.7%, 49.0%, respectively), followed by 4Q DBH (5.9%, 34.7%, 40.8%) and venous beading (5.0%, 17.2%, 39.9%) (Figure 2).

The presence of IRMA was associated with 1.77-fold higher chance of developing PDR than venous beading in 2 quadrants (95% CI 1.25–2.49) after adjusting for age, sex, race, and initial VA. A similar trend was seen with 4Q DBH, but this was not statistically significant (HR 1.47, 95% CI 0.94–2.31) (Figure 2) (Table 2).

PROGRESSION TO VITREOUS HEMORRHAGE BY DIABETIC RETINOPATHY SEVERITY

The percentages of progression to VH by years 1, 3, and 5 per baseline DR were as follows: no DR (0.3%, 0.7%, 1.1%, respectively), very mild (0.2%, 0.8%, 1.8%), mild (0.3%, 1.3%, 2.9%), moderate (0.6%, 3.3%, 7.3%), severe (0.9%, 4.7%, 9.8%), and very severe NPDR (3.0%, 10.9%, 17.8%) (Figure 3).

In comparison to patient eyes with no DR, the eyes with very mild NPDR at baseline were 1.68 times more likely to progress to VH (95% CI 1.24–2.27), while mild, moderate, severe, and very severe NPDR were 2.56 (95% CI 1.91–3.42), 5.60 (95% CI 4.26–7.36), 7.29 (95% CI 5.41–9.84), and 12.6 times more likely to develop VH (95% CI 9.03–17.6), respectively, after adjusting for age, sex, race, and initial VA (Table 2).

PROGRESSION TO VITREOUS HEMORRHAGE BY DIABETIC RETINOPATHY FEATURES

In subanalysis that included only patient eyes with severe NPDR (n = 2823), the rates of progression to VH by years 1, 3, and 5 were highest in eyes with baseline 4Q DBHs (4.5%, 7.3%, 13.8%), followed by IRMA (0.3%, 2.2%, 9.7%) and venous beading (1.3%, 4.3%, not available) (Figure 4).

When comparing the risks associated with specific clinical features, a 3.84-fold statistically significant increase in hazard of developing VH (95% CI 1.39–10.6) was associated with the presence of 4 quadrants of DBH compared with venous beading. Near 50% increase with IRMA was seen compared with venous beading, but this was not statistically significant (HR 1.42, 95% CI 0.44–3.66) (Figure 4) (Table 2).

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ANALYSES WITH 1 EYE SELECTION

To rule out any significant effect for bilateral eye correlation, only 1 eye was randomly selected per patient and analyses were repeated. The results did not change significantly: compared with no DR, the hazard of progressing to PDR from mild NPDR was 6.56 (95% CI 5.06–8.51), and from moderate and severe NPDR were 13.9 (95% CI 10.8–17.9) and 26.5 (95% CI 20.5–34.4), respectively. Compared with venous beading, the eyes with IRMA and 4Q DBH were 1.57 (95% CI 1.06–2.31) and 1.15 (95% CI 0.67–1.97) more likely to progress to PDR, respectively. Regarding the progression to VH, mild NPDR had 2.63 (95% CI 1.81–3.81) times higher hazard, while moderate and severe NPDR had 5.43 (95% CI 3.82–7.71) and 7.66 (95% CI 5.25–11.2) higher HR compared with no DR, respectively. The hazard of progressing to VH in the eyes with 4Q DBH and IRMA were 4.25 (95% CI 1.32–13.6) and 1.53 (95% CI 0.54–4.36) higher than venous beading, respectively.

DISCUSSION

This Paper Demonstrates that more than 20 years after the original Airlie House classification and ETDRS studies, baseline severity of DR continues to predict patients' clinical outcomes. Approximately 44%–56% of patients with severe or very severe NPDR progressed to PDR or VH in less than 3 years. Among 3 main clinical features of severe NPDR (4Q DBH, IRMA, and venous beading), the most significant feature predictive of PDR progression was IRMA, whereas the presence of 4Q DBH was the most significant risk factor for VH.

The prevalence of DR in our hospital eye clinic–based study population was 72.4% at initial examination, with very mild and mild NPDR being the most common. Severe DR was more common in younger men. The UK has a community-based whole-population retinopathy screening program for people with diabetes.[17] Patients with diabetes in the hospital eye services have therefore been referred by their local screening program owing to an increased risk of sight-threatening DR, DME, or another ocular condition (eg, cataract or glaucoma). Thus, the finding of nearly 30% of no DR may be explained by patients with unilateral DR/DME or who have been referred owing to other ocular conditions.

Previous epidemiology studies have reported varying rates of progression to PDR. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) reported a 9% rate of progression to PDR over 4 years in patients who present with early retinopathy at baseline.[6] A UK cohort of 20 686 patients without PDR or maculopathy at initial DR screening between 1990 and 2006 showed an 11% cumulative incidence of PDR at 10 years among 3632 patients with NPDR at baseline.[7] The Beijing Eye Study of 170 subjects showed a 35% overall progression rate in subjects with baseline DR and 21% in patients with no baseline retinopathy during the 2001 to 2006 period.[18] Other studies have shown rates of progression to PDR ranging from 5.3% to 8.2% at 4–9 years of follow-up in patients with baseline mild or unspecified severities of NPDR.[8–10]

In contrast to epidemiologic studies, data from clinical trials originate from much smaller sample sizes and similarly variable results. ETDRS, one of the largest clinical trials, including a total of 3711 patients between 1980 and 1985, showed 65.3%–82.8%

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progression rate from severe NPDR to PDR in 5 years[4]; however, its study period predates most current standards of care for retinopathy.[19] More recently, the RISE and RIDE trials recruited 377 and 382 patients, respectively, to compare the treatment outcomes of patients with diabetic macular edema.[20] Fewer than 150 patients that were treated with sham injection provide the progression data and 8.7%–10.5% rates of progression of ≥2 steps in 2 years were reported. Similarly, a 12.3% incidence of 2-step progression was found in the placebo arm (1012 patients) of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study during 5-year follow-up.[21] In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, which included 2856 patients, the control group had a 10.4% rate of ≥3-step progression during 4-year follow-up.[22] A 20% rate of 2-step progression was found in 595 patients with baseline retinopathy during 5 years in the Veterans Affairs Diabetes Trial (VADT).[23]

Our progression rates were lower than in ETDRS but slightly higher than the rates reported in more recent population studies and randomized controlled trials.[7–10] A meta-analysis that included 27 120 diabetic patients from 28 studies showed pooled incidence of PDR of 11.0% in 4 years.[24] Interestingly, when stratified for time period, the 4-year incidence of PDR was 19.5% in 1975–1985 and 2.6% in 1986–2008, indicating improved diabetic care in recent years. Thus, our cohort's lower progression rate than ETDRS is not surprising. In addition, our study population's higher progression rate than more recent studies could likely be explained by a selection bias. All our patients were referred from community DR screening centers and we would expect our study population to be enriched for patients with more severe baseline retinopathy and who are therefore at a greater risk of progression. In addition, the rate differences between our study and others may include the varying diabetic control status of the study population, the cohort bias owing to varying study generations, and changing patterns in diabetic care that could have led to different incidences of PDR.

The simplified features of severe NPDR were largely defined from landmark trials such as DRS and ETDRS. Our study demonstrates that the presence of 4Q DBH and IRMA are significantly more predictive of progression than venous beading. Interestingly, although IRMA was the most important risk factor predictive of PDR progression, the risk of VH was higher in patients with 4Q DBH compared with those with IRMA or venous beading. IRMA has been shown to be a precursor of neovascularization elsewhere (NVE) in a longitudinal case evaluation with spectral-domain optical coherence tomography (OCT),[25] and this likely explains why IRMA was the most predictive of PDR. A possible explanation for the disconcordance in the risk factor for PDR vs VH is that IRMA may lead to NVEs that are less likely to hemorrhage than 4Q DBH. Given that venous beading does not appear as critical as the other 2 features in predicting PDR or VH, and because IRMA vs NVE can be distinguished with OCT,[25] the evaluation of venous beading with or without fluorescein angiography may become less important in the future if validated in other cohorts. It may also indicate that ophthalmologists in real-world settings record IRMA and VH more routinely or reliably than venous caliber change.

Our study suggests that current screening guidelines of at least an annual screening examination for all patients with diabetes may not detect new cases of PDR as often as previously thought, although screening also serves the purpose of detecting DME.[26] Only

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2.3%–8.6% of patient eyes that had no DR or very mild NPDR and had not required anti-VEGF treatment progressed to PDR in 5 years. Similarly, the 4-year incidence of PDR in patients with no baseline DR was 2.8% (33/1164) in a meta-analysis that included 14 studies conducted during 1986 and 2008.[24] Nevertheless, 0.3%–0.8% of these eyes progressed to PDR in 1 year, suggesting that more specific, feature-based criteria would be advantageous in determining the appropriate frequency of follow-up. Our study findings need to be replicated and validated in future studies prior to recommending different intervals; however, this highlights the importance of understanding varying risks of individual clinical features when evaluating patients with severe DR, which may result in different follow-up frequency for each individual patient or different systemic or ocular treatment algorithms.

Our study results may not be generalizable to other populations of different income settings beyond the UK. Other countries may differ in baseline rate of diabetes or quality of diabetes control. Nevertheless, the results reveals that IRMA and hemorrhages are still key clinical signs (which can be diagnosed on clinical examination or photography) with respect to progression to PDR/VH; therefore, these features should be highlighted when training staff (technicians, nurses, physicians) involved in DR screening in any setting or countries. Future studies on the effect of clinical features in DR progression in different settings will provide further insights.

The main strengths of our paper include a large sample size with granularity of the clinical data above what is available in a conventional free-test EMR. However, the main limitation is that our data are dependent on the quality of each examination and recording in EMR. Our study EMR demonstrated ETDRS standard photographs next to the clinical examination section to improve each physician’s examination, and all participating retina physicians were instructed to complete all sections of structured data entry as mandated fields when diabetic retinopathy grading was performed. However, our examination results do not originate from stereoscopic photograph evaluations in a reading center such as in randomized controlled trials, and thus may differ from other clinical trials. Nevertheless, large epidemiologic or clinical studies are becoming increasingly more difficult and costly to perform, and the results of real-world practice provide equally important, but different information. Future studies to assess the quality and reliability of fundus grading in the study EMR will be valuable.

Additional limitations include unknown status of confounders such as type of diabetes and level of hyperglycemia and hypertension in our patients.[27] The type of diabetes mellitus (I or II) may influence the risk of PDR and VH differently, but this information was not recorded in our EMR. In addition, our study did not include patients who received anti-VEGF, which likely affects the rate of DR progression.[28] Further stratified analyses of DR progression in patient eyes with or without DME are planned in our subsequent report.

Proliferative diabetic retinopathy and vitreous hemorrhage are important endpoints of sight-threatening diabetic retinopathy. Our study demonstrates that baseline diabetic retinopathy severities and clinical features of initial diabetic retinopathy screening remain key prognostic factors. The EMR-facilitated feature-based evaluations of diabetic retinopathy provide not

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only a large cohort of patients for epidemiologic study but also the basis for large clinical studies in which important outcome predictors can be assessed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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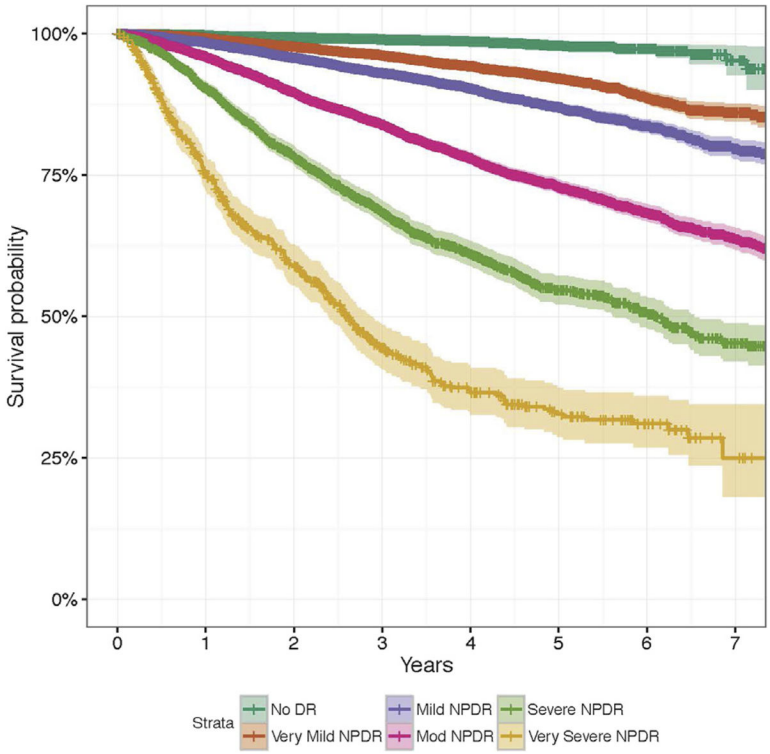

FIGURE 1.

Kaplan-Meier curves on survival analyses in progression to proliferative diabetic retinopathy (PDR), stratified by severity of diabetic retinopathy (DR) at initial evaluation. Time to PDR is associated with baseline DR severity after adjusting for age, sex, race, and starting visual acuity. x-axis: time in years; y-axis: percentage of patient eyes at risk. NPDR = nonproliferative diabetic retinopathy. Shaded areas represent 95% confidence intervals.

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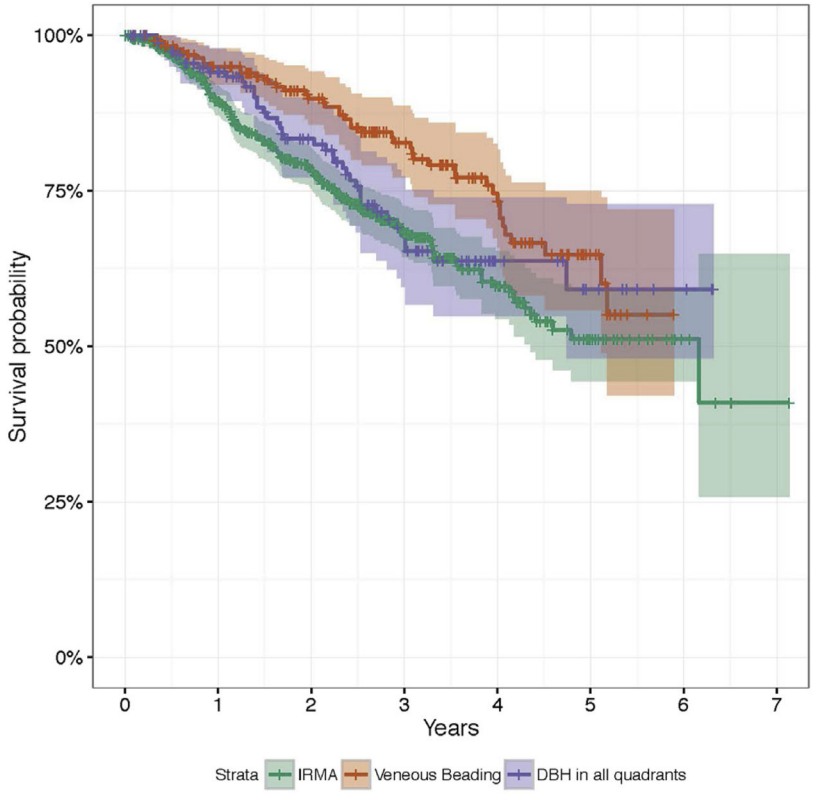

FIGURE 2.

Kaplan-Meier curves on survival analyses in progression to proliferative diabetic retinopathy (PDR), stratified by presence of different clinical features at initial evaluation. Compared with the eyes with venous beading, the eyes with intraretinal microvascular abnormalities (IRMA) had a significantly increased risk of developing PDR. x-axis: time in years; y-axis: percentage of patient eyes at risk. DBH = dot-blot hemorrhages. Shaded areas represent 95% confidence intervals.

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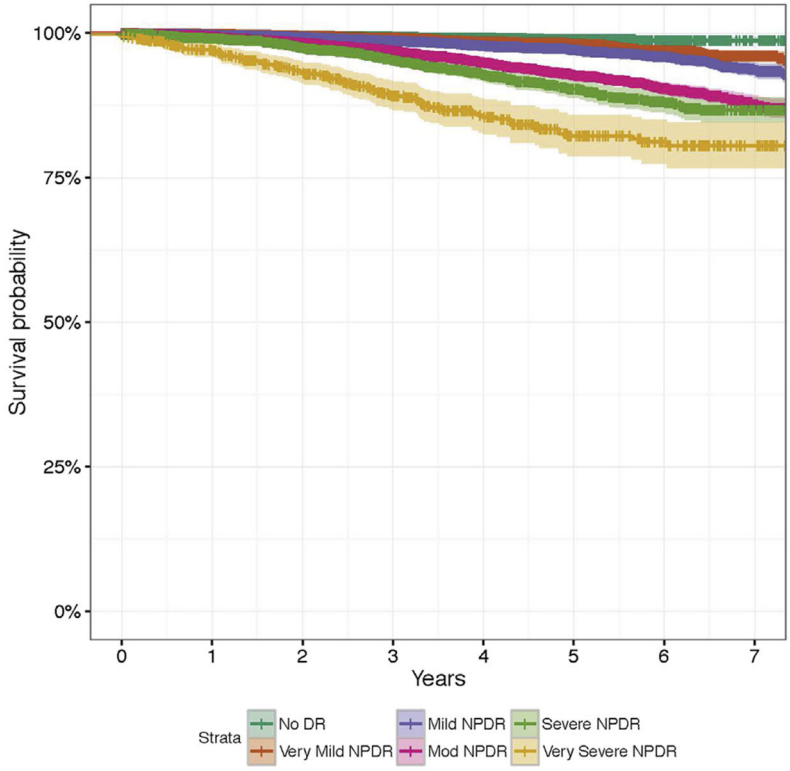

FIGURE 3.

Kaplan-Meier curves on survival analyses in progression to vitreous hemorrhage (VH), stratified by severity of diabetic retinopathy (DR) at initial evaluation. Time to VH is associated with baseline DR stage after adjusting for age, sex, race, and starting visual acuity. x-axis: time in years; y-axis: percentage of patient eyes at risk. NPDR = nonproliferative diabetic retinopathy. Shaded areas represent 95% confidence intervals.

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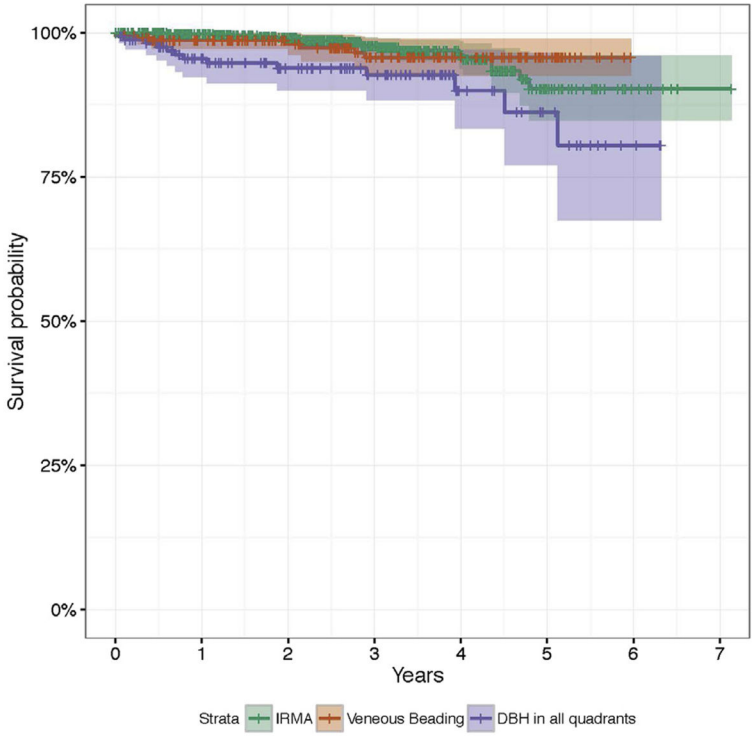

FIGURE 4.

Kaplan-Meier curves on survival analyses in progression to vitreous hemorrhage (VH), stratified by presence of different clinical features at initial evaluation. Compared with the eyes with venous beading, the eyes with 4-quadrant dot-blot hemorrhages had a significantly increased risk of developing VH. x-axis: time in years; y-axis: percentage of patient eyes at risk. DBH = dot-blot hemorrhage; IRMA = intraretinal microvascular abnormalities. Shaded areas represent 95% confidence intervals.

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TABLE 1

Demographic and Baseline Clinical Characteristics of Patient Eyes

	No DR	Very Mild NPDR	Mild NPDR	Moderate NPDR	Severe NPDR	Very Severe NPDR	Total
N	16 762	16 081	12 856	10 909	2823	823	60 254
Age (SD)	71.75 (13.74)	63.46 (15.24)	63.00 (14.72)	60.99 (14.95)	50.00 (14.90)	57.98 (14.77)	64.89 (15.31)
Male (%)	8126 (48.47)	9001 (56.03)	7487 (58.24)	6468 (59.29)	1779 (63.04)	496 (60.27)	33 366 (55.38)
Caucasian, n (%)	11 487 (68.52)	9941 (61.82)	7795 (60.63)	6986 (64.04)	1764 (62.51)	569 (69.14)	38 542 (63.97)
Right eye, n (%)	8373 (49.95)	7938 (49.36)	6480 (50.40)	5480 (50.23)	1419 (50.28)	402 (48.85)	30 092 (49.94)
Mean VA (SD)	67.14 (25.68)	74.97 (17.79)	74.42 (17.19)	84.89 (16.62)	74.17 (18.06)	71.09 (20.36)	72.60 (20.30)

DR = diabetic retinopathy; NPDR = nonproliferative diabetic retinopathy; SD = standard deviation; VA = visual acuity (Early Treatment Diabetic Retinopathy Study).

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TABLE 2

Multivariate Cox Regression Analyses on Progression to Proliferative Diabetic Retinopathy or Vitreous Hemorrhage

	Progression to PDR			**Progression to VH**		
	HR	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Age	0.98	0.97–0.98	$<2 \times 10^{-16}$	0.98	0.97–0.98	$<2 \times 10^{-16}$
Sex	0.95	0.89–1.01	.093	1.08	0.96–1.23	.20
Non-Caucasian	0.94	0.89–1.00	.65	0.76	0.66–0.87	6.80×10^{-5}
VA	0.99	0.98–0.99	$<2 \times 10^{-16}$	0.98	0.98–0.98	$<2 \times 10^{-16}$
DR level						
No DR	Ref			Ref		
Very mild NPDR	4.02	3.25–4.96	$<2 \times 10^{-16}$	1.68	1.24–2.27	8.1×10^{-4}
Mild NPDR	6.71	5.46–8.24	$<2 \times 10^{-16}$	2.56	1.91–3.42	2.36×10^{-10}
Moderate NPDR	14.80	12.10–18.09	$<2 \times 10^{-16}$	5.60	4.26–7.36	$<2 \times 10^{-16}$
Severe NPDR	28.19	22.92–34.67	$<2 \times 10^{-16}$	7.29	5.41–9.84	$<2 \times 10^{-16}$
Very severe NPDR	58.42	46.95–72.70	$<2 \times 10^{-16}$	12.60	9.03–17.57	$<2 \times 10^{-16}$
	Progression to PDR			Progression to VH		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age	0.99	0.98–0.99	.0056	0.97	0.95–0.99	.039
Sex	0.92	0.71–1.19	.53	1.20	0.60–2.40	.61
Non-Caucasian	1.01	0.77–1.31	.96	0.76	0.27–1.59	.47
VA	0.99	0.98–0.99	1.60×10^{-5}	0.97	0.96–0.98	2.55×10^{-13}
DR feature						
Venous beading	Ref			Ref		
4 quadrants DBH	1.47	0.94–2.31	.88	3.84	1.39–10.62	.0095
IRMA	1.77	1.25–2.49	.0013	1.42	0.55–3.66	.47

CI = confidence interval; DBH = >2A dot-blot hemorrhages; DR = diabetic retinopathy; HR = hazard ratio; IRMA = inner retinal microvascular abnormalities; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; VA = visual acuity; VH = vitreous hemorrhage.