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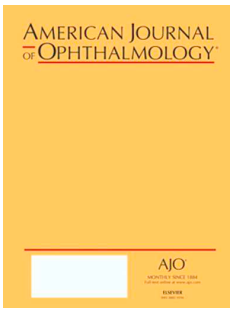

The United Kingdom Diabetic Retinopathy Electronic Medical Record Users Group: Report 3: Baseline Retinopathy and Clinical Features Predict Progression of Diabetic Retinopathy

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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, gender, 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 non-proliferative 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 to 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% CI 1.25-2.49, p=0.0013) compared to those with venous beading, while those with 4 quadrant dot blot hemorrhages (4Q DBHs) had 3.84 higher HR of developing VH (95% CI 1.39-10.62, p=0.0095).

Conclusions: Baseline severities and features of initial DR are prognostic for PDR development. IRMA increases risk of PDR while 4Q DBHs increases risk of VH.

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Running Head: Feature-based evaluation of diabetic retinopathy progression

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Short title
Baseline severities and features of DR predict progression.

Abbreviations
4Q DBH: four quadrant dot blot hemorrhage
DBH: dot blot hemorrhage
DME: diabetic macular edema
DR: diabetic retinopathy
DRS: Diabetic Retinopathy Study
EMR: electronic medical record
ETDRS: Early Treatment Diabetic Retinopathy Study
FA: fluorescein angiography
IRMA: intraretinal microvascular abnormalities
NA: not applicable
NHS: National Health Service
NPDR: non-proliferative diabetic retinopathy
NVE: neovascularization elsewhere
OCT: optical coherence tomography
PDR: proliferative diabetic retinopathy
RCT: randomized controlled trial
UK: United Kingdom
UK DR EMR: United Kingdom Diabetic Retinopathy Electronic Medical Record
VA: visual acuity
VEGF: vascular endothelial growth factor
VH: vitreous hemorrhage
WESDR: Wisconsin Epidemiologic Study of Diabetic Retinopathy

INTRODUCTION

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 US alone.[2] Even though early detection of DR can substantially decrease the risk of blindness, the non-adherence rate of diabetic retinopathy 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 non-proliferative diabetic retinopathy (NPDR) to proliferative diabetic retinopathy (PDR) is approximately 52% in one 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 in 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 explored with real world data. This information will be important in guiding follow-up intervals on monitoring for diabetic retinopathy, advising the patient and their diabetic care team regarding progression risk, as well as 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), two 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 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 was extracted through the EMR compulsory DR structured assessment module as described previously.[16] Demographic data was 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 26th, 2014.

EMR 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] photos for IRMA and DBH, respectively. The following non-proliferative 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, MA only, hemorrhages <next level, >=4 blot hemorrhages in any quadrant and >=8 in total, >=2a in any quadrant, >2a in all quadrant), 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: microaneurysms (MA) only, hemorrhages/microaneurysms < standard ETDRS photograph 2a[4], $\geq$ 4 dot blot hemorrhages (DBHs) in any quadrants and $\geq$ 8 in total, DBHs > standard ETDRS photograph 2a[4] in any quadrant, DBHs > standard ETDRS photograph 2a[4] in all quadrants, intraretinal microvascular abnormalities (IRMA) $\geq$ 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-Meyer 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, gender, presenting visual acuity 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 one 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 64,225 eyes (33,598 patients) were identified with a structured DR assessment. 13,971 eyes (1,045 patients) were excluded due to anti-VEGF injections. A total of 50,254 patient eyes (32,553 patients) were included in the study. The mean age was 64.89 (IQR 55.10 to 76.68), and 63.97% were Caucasian. The overall mean presenting visual acuity was 72.60 ETDRS letters (IQR 70.0 to 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 DR Severity

The percentages of progression to PDR by year 1, 3, 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).

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

Progression to Proliferative Diabetic Retinopathy by DR 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 with 4Q DBHs were found. In this group, the percentages of progression to PDR by year

1, 3, 5 were highest in patient eyes with IRMA (10.5%, 31.7%, 49.0%, respectively), followed by 4Q DBHs (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 two quadrants (95%CI 1.25 to 2.49) after adjusting for age, gender, race, and initial VA. Similar trend was seen with 4Q DBHs but this was not statistically significant (HR 1.47, 95%CI 0.94 to 2.31) (Figure 2) (Table 2).

Progression to Vitreous Hemorrhage by DR Severity

The percentages of progression to VH by year 1, 3, 5 per baseline DR were the following: 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% 1.24 to 2.27) while mild, moderate, severe, and very severe NPDR were 2.56 (95%CI 1.91 to 3.42), 5.60 (95%CI 4.26 to 7.36), 7.29 (95%CI 5.41 to 9.84), 12.6 times more likely to develop VH (95%CI 9.03 to 17.6), respectively after adjusting for age, gender, race, and initial VA (Table 2).

Progression to Vitreous Hemorrhage by DR features

In subanalysis that included only patient eyes with severe NPDR (n=2823), the rates of progression to VH by year 1, 3, 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%, NA) (Figure 4).

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

Analyses with One Eye Selection

To rule out any significant effect for bilateral eye correlation, only one eye was randomly selected per patient and analyses were repeated. The results did not change significantly: compared to no DR, the hazard of progressing to PDR from mild NPDR was 6.56 (95%CI 5.06 to 8.51), while from moderate and severe NPDR were 13.9 (95%CI 10.8 to 17.9) and 26.5 (95%CI 20.5 to 34.4), respectively. Compared to venous beading, the eyes with IRMA and 4Q DBH were 1.57 (95%CI 1.06 to 2.31) and 1.15 (95%CI 0.67 to 1.97) more likely to progress to PDR, respectively. Regarding the progression to VH, mild NPDR had

2.63 (95%CI 1.81 to 3.81) times higher hazard, while moderate and severe NPDR had 5.43 (95%CI 3,82 to 7.71) and 7.66 (95%CI 5.25 to 11.2) higher HR compared to no DR, respectively. The hazard of progressing to VH in the eyes with 4Q DBH and IRMA were 4.25 (95%CI 1.32 to 13.6) and 1.53 (95%CI 0.54 to 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 proliferative diabetic retinopathy or vitreous hemorrhage in less than three years. Among three main clinical features of severe NPDR (4Q DBHs, IRMA, and venous beading), the most significant feature predictive of PDR progression was IRMA, while the presence of 4Q DBHs 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 due to an increased risk of sight-threatening DR, DME, or for another ocular condition e.g. 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 due to other ocular conditions.

Previous epidemiology studies have reported varying rates of progression to PDR. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) reported 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 2001 to 2006 period.[18] Other studies have shown rates of progression to PDR ranging from 5.3% to 8.2% at 4 to 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, included a total of 3711 patients between 1980 and 1985, showed 65.3-82.8% 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, RISE and RIDE trials recruited 377 and 382 patients, respectively, to

compare the treatment outcomes of patients with diabetic macular edema.[20] Less than 150 patients that were treated with sham injection provide the progression data and 8.7-10.5% rate 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% 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 RCTs.[7-10]A meta-analysis that included 27,120 diabetic patients from 28 studies showed pooled incidence of PDR 11.0% in 4 years.[24] Interestingly, when stratified for time period, the incidence of PDR was 19.5% in 1975-1985 while 2.6% in 1986-2008 in 4 years, 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 therefore at a greater risk of progression. In addition, the rate differences between our study and others may include varying diabetic control status of the study population, the cohort bias due to varying study generations, and changing patterns in diabetic care that could have led to different incidence 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 DBHs and IRMA are significantly more predictive of progression than venous beading. Interestingly, while IRMA was the most important risk factor predictive of PDR progression, the risk of VH was higher in patients with 4Q DBHs compared to 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] thus 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 DBHs. Given that venous beading does not appear as critical as the other two features in predicting PDR or VH, and since IRMA vs. NVE can be distinguished with OCT,[25] the evaluation of venous beading with or without FA may become a less important in 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 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 feature 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 IRMAs 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 clinical features in DR progression in different settings will provide further insights.

The main strengths of our paper include 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 is dependent on the quality of each examination and recording in EMR. Our study EMR demonstrated ETDRS standard photos next to the clinical exam 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 exam results do not originate from stereoscopic photo evaluations in a reading center such as in RCTs, 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, 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 provides not only a large cohort of patients for epidemiological study but also the basis for large clinical studies in which important outcome predictors can be assessed.

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b. Financial Disclosures
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FIGURE CAPTIONS

Figure 1. Kaplan-Meyer 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, gender, race, and starting visual acuity. x-axis, time in year. y-axis; percentage of patient eyes at risk; NPDR, non-proliferative diabetic retinopathy. Shaded areas represent 95% confidence intervals.

Figure 2.Kaplan-Meyer curves on survival analyses in progression to proliferative diabetic retinopathy (PDR), stratified by presence of different clinical features at initial evaluation. Compared to the eyes with venous beading, the eyes with intraretinal microvascular abnormalities (IRMA) had a significantly increased risk of developing PDR. x-axis, time in year. y-axis; percentage of patient eyes at risk; IRMA, intraretinal microvascular abnormalities; DBH, dot blot hemorrhages. Shaded areas represent 95% confidence intervals.

Figure 3.Kaplan-Meyer 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, gender, race, and starting visual acuity. x-axis, time in year. y-axis; percentage of patient eyes at risk; NPDR, non-proliferative diabetic retinopathy. Shaded areas represent 95% confidence intervals.

Figure 4.Kaplan-Meyer curves on survival analyses in progression to vitreous hemorrhage (VH), stratified by presence of different clinical features at initial evaluation. Compared to 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 year. y-axis; percentage of patient eyes at risk; IRMA, intraretinal microvascular abnormalities; DBH, dot blot hemorrhages. Shaded areas represent 95% confidence intervals.

Table 1. Demographic and Baseline Clinical Characteristics of Patient Eyes.

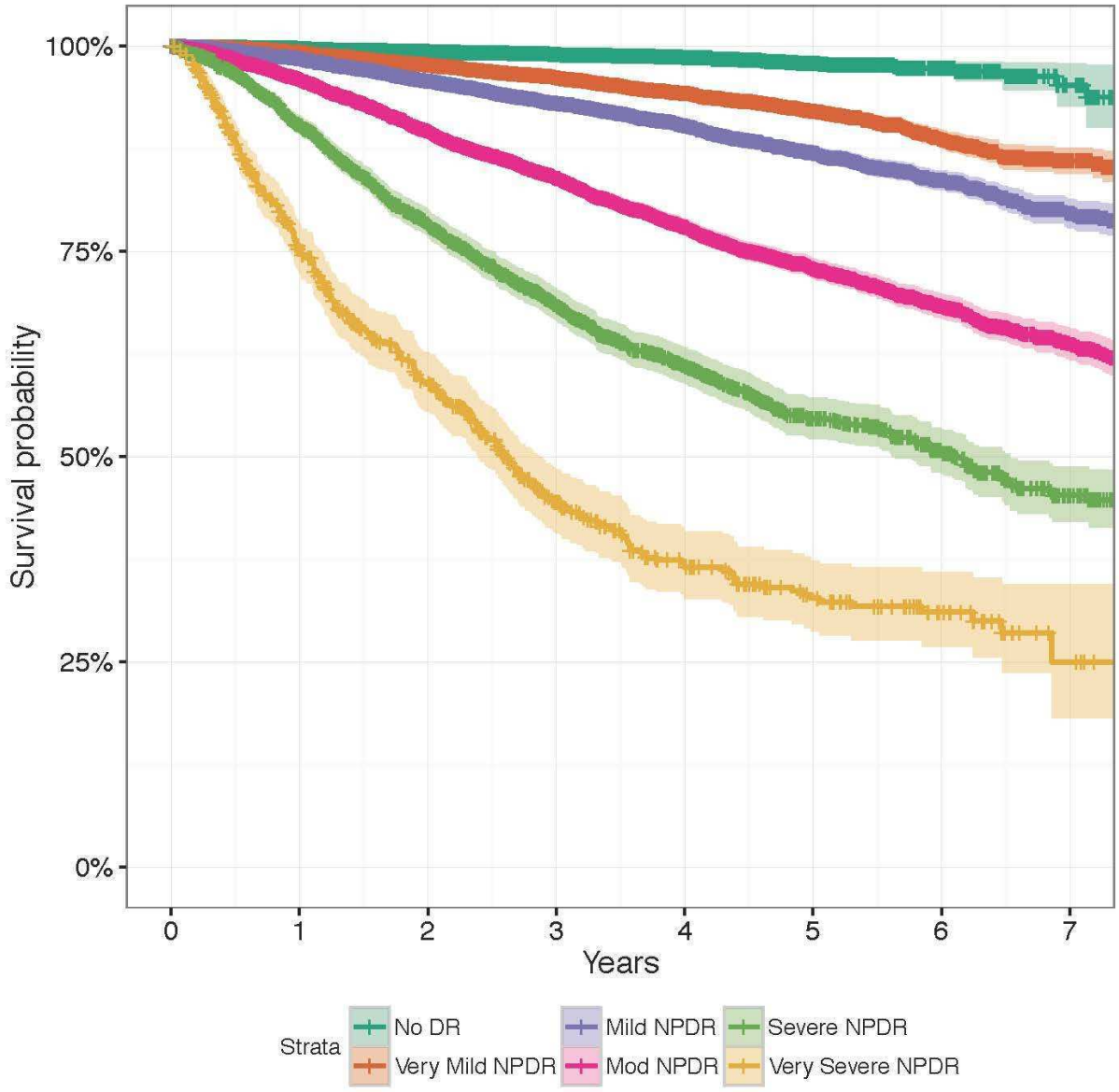
	No DR		Very Mild NPDR		Mild NPDR		Moderate NPDR		Severe NPDR		Very Severe NPDR		Total	
n	16762		16081		12856		10909		2823		823		50254	
Age (SD)	71.75	13.74	63.46	15.24	63.00	14.72	60.99	14.95	50.00	14.90	57.98	14.77	64.89	15.31
Male (%)	8126	48.47	9001	56.03	7487	58.24	6468	59.29	1779	63.04	496	60.27	33366	55.38
Caucasian (%)	11487	68.52	9941	61.82	7795	60.63	6986	64.04	1764	62.51	569	69.14	38542	63.97
Right eye (%)	8373	49.95	7938	49.36	6480	50.40	5480	50.23	1419	50.28	402	48.85	30092	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

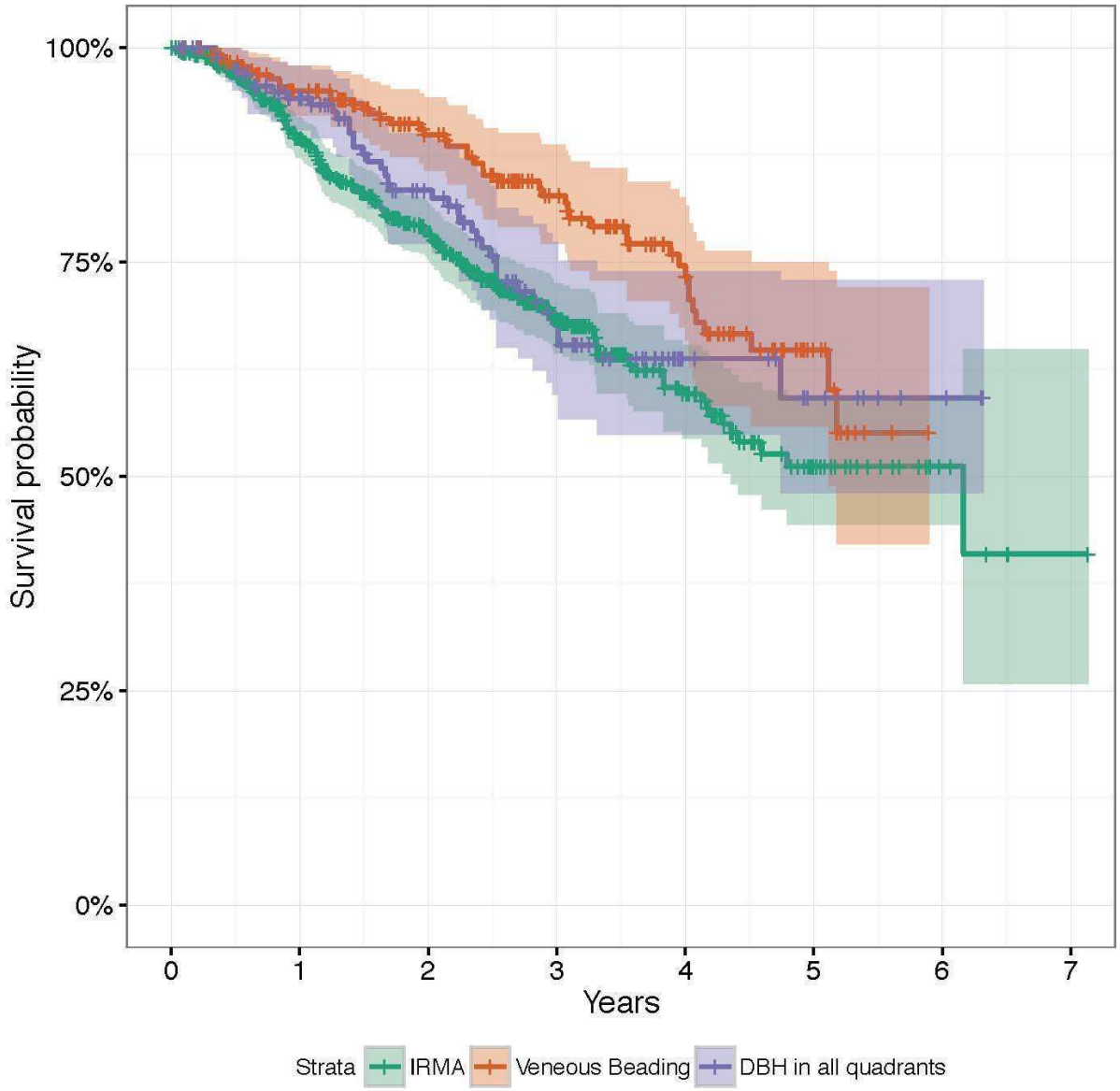
DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; SD, standard deviation; VA, visual acuity (Early Treatment Diabetic Retinopathy Study).

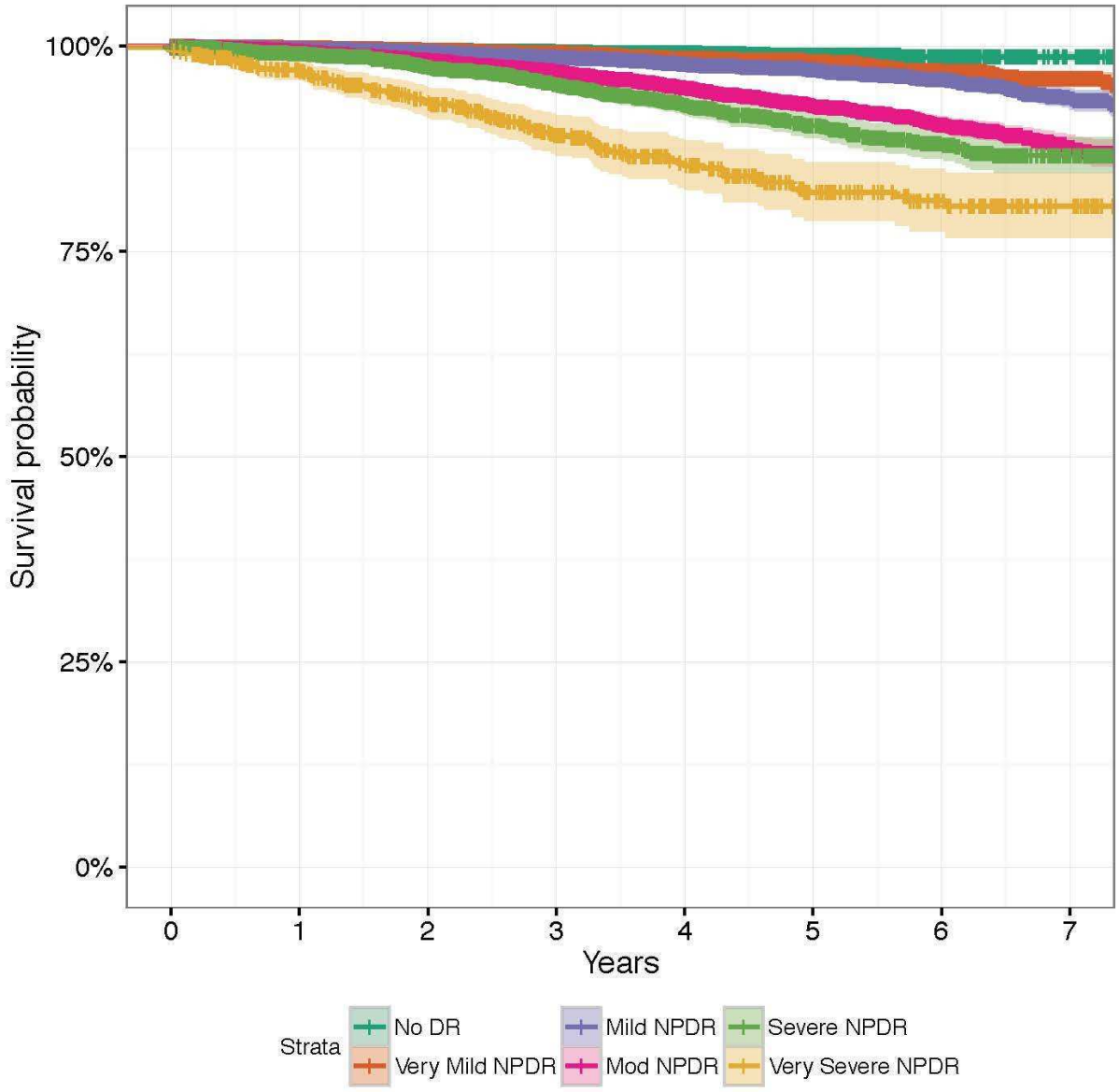
Table 2. Multivariate Cox Regression Analyses on Progression to Proliferative Diabetic Retinopathy or Vitreous Hemorrhage.

	Progression to PDR				Progression to VH			
	HR	95% CI		p value	HR	95% CI		p value
Age	0.98	0.97	0.98	$< 2x10^{-16}$	0.98	0.97	0.98	$< 2x10^{-16}$
Gender	0.95	0.89	1.01	0.093	1.08	0.96	1.23	0.20
Non-caucasian	0.94	0.89	1.00	0.65	0.76	0.66	0.87	$6.80 x10^{-5}$
VA	0.99	0.98	0.99	$< 2x10^{-16}$	0.98	0.98	0.98	$< 2x10^{-16}$
DR level								
no DR	Ref				Ref			
very mild NPDR	4.02	3.25	4.96	$< 2x10^{-16}$	1.68	1.24	2.27	$8.1 x10^{-4}$
mild NPDR	6.71	5.46	8.24	$< 2x10^{-16}$	2.56	1.91	3.42	$2.36x10^{-10}$
moderate NPDR	14.80	12.10	18.09	$< 2x10^{-16}$	5.60	4.26	7.36	$< 2x10^{-16}$
severe NPDR	28.19	22.92	34.67	$< 2x10^{-16}$	7.29	5.41	9.84	$< 2x10^{-16}$
very severe NPDR	58.42	46.95	72.70	$< 2x10^{-16}$	12.60	9.03	17.57	$< 2x10^{-16}$
	Progression to PDR				**Progression to VH**			
	HR	95% CI		p value	HR	95% CI		p value
Age	0.99	0.98	0.99	0.0056	0.97	0.95	0.99	0.039
Gender	0.92	0.71	1.19	0.53	1.20	0.60	2.40	0.61
Non-caucasian	1.01	0.77	1.31	0.96	0.76	0.27	1.59	0.47
VA	0.99	0.98	0.99	$1.60x10^{-5}$	0.97	0.96	0.98	$2.55x10^{-13}$
DR Feature								
Venous beading	Ref				Ref			
4 quadrants DBH	1.47	0.94	2.31	0.88	3.84	1.39	10.62	0.0095
IRMA	1.77	1.25	2.49	0.0013	1.42	0.55	3.66	0.47

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


100%
75%
50%
25%
0%
Survival probability
0
1
2
3
4
5
6
7
Years
Strata
No DR
Very Mild NPDR
Mild NPDR
Mod NPDR
Severe NPDR
Very Severe NPDR


100%
75%
50%
25%
0%
Survival probability
0
1
2
3
4
5
6
7
Years
Strata
IRMA
Veneous Beading
DBH in all quadrants


100%
75%
50%
25%
0%
Survival probability
0
1
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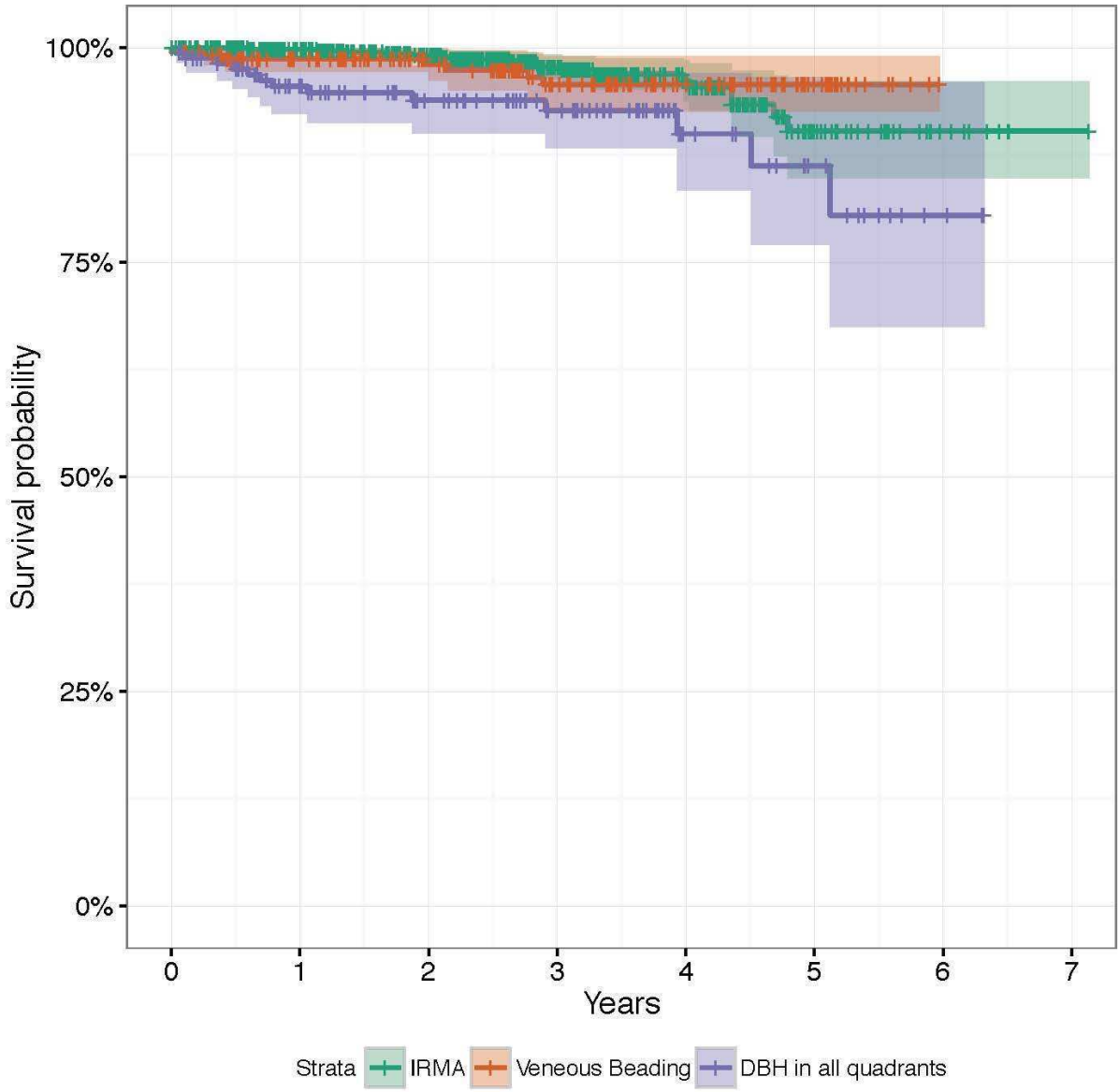
Years
Strata
No DR
Very Mild NPDR
Mild NPDR
Mod NPDR
Severe NPDR
Very Severe NPDR


100%
75%
50%
25%
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Survival probability
0
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Years
Strata
IRMA
Veneous Beading
DBH in all quadrants