Predicting Development of Proliferative Diabetic Retinopathy

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OBJECTIVE—Identifying individuals most at risk for diabetic retinopathy progression and intervening early can limit vision loss and reduce the costs associated with managing more advanced disease. The purpose of this study was to identify factors associated with progression from nonproliferative diabetic retinopathy (NPDR) to proliferative diabetic retinopathy (PDR).

RESEARCH DESIGN AND METHODS—This was a retrospective cohort analysis using a claims database of all eye care recipients age ≥30 years enrolled in a large managed-care network from 2001 to 2009. Individuals with newly diagnosed NPDR were followed longitudinally. Multivariable Cox regression analyses identified factors associated with progression to PDR. Three- and five-year probabilities of retinopathy progression were determined.

RESULTS—Among the 4,617 enrollees with incident NPDR, 307 (6.6%) developed PDR. After adjustment for confounders, every 1-point increase in HbA_{1c} was associated with a 14% (adjusted hazard ratio 1.14 [95% CI 1.07–1.21]) increased hazard of developing PDR. Those with nonhealing ulcers had a 54% (1.54 [1.15–2.07]) increased hazard of progressing to PDR, and enrollees with nephropathy had a marginally significant increased hazard of progressing to PDR (1.29 [0.99–1.67]) relative to those without these conditions. The 5-year probability of progression for low-risk individuals with NPDR was 5% (range 2–8) and for high-risk patients was 38% (14–55).

CONCLUSIONS—Along with glycemic control, nonophthalmologic manifestations of diabetes mellitus (e.g., nephropathy and nonhealing ulcers) are associated with an increased risk of diabetic retinopathy progression. Our retinopathy progression risk score can help clinicians stratify patients who are most at risk for disease progression.

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D iabetic retinopathy is the leading cause of new cases of legal blindness in the U.S. (1), affecting 4.2 million Americans, 655,000 of whom have sight-threatening retinopathy (1,2). Identifying patients who are at increased risk of progression from nonproliferative (NPDR) to proliferative diabetic retinopathy (PDR) is important for many reasons. From the patient's perspective, individuals who progress from NPDR to PDR frequently experience a decline in best-corrected visual acuity, which can have a profound impact on health-related quality of life (3). In addition, those who develop PDR are at substantially increased risk of serious complications

that can result in permanent vision loss such as tractional retinal detachment, vitreous hemorrhage, and neovascular glaucoma (4,5). From a societal perspective, the costs of caring for patients with PDR are four times greater than the costs of managing patients with NPDR. One study found the average cost of caring for patients with NPDR to be 292 USD, while it cost 1,207 USD to manage patients who develop PDR (6). Another study conducted by the National Health Services in Taiwan found that individuals who progressed from NPDR to PDR were noted to have an increase in expenditures of 3,482 USD (7). The ability for clinicians to identify and treat patients early

in the disease process, before they experience progression to PDR, may result in considerable cost savings, especially in light of the growing number of individuals with diabetes mellitus (DM) in the U.S. population.

In patients with DM, metabolic control as measured by HbA_{1c} and disease duration account for only 11% of the risk of retinopathy, leaving 89% to other factors (8). Several large population-based studies including the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), the UK Prospective Diabetes Study (UKPDS), and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study have identified other risk factors associated with the development or progression of diabetic retinopathy (9–11). From the results of these studies, age, sex, socioeconomic status, and comorbid systemic arterial hypertension are considered important determinants of retinopathy risk. We are unaware of any studies in the literature that have integrated these and other factors into a comprehensive diabetic retinopathy risk score that can help clinicians identify individuals who are at increased risk of progression from NPDR to PDR. Risk calculators such as the Framingham Risk Score for Atrial Fibrillation (12) and the Ocular Hypertension Treatment Study risk calculator (13) have been found to be useful in aiding clinicians with patient decision making.

The purpose of this analysis was to assess risk factors associated with progression of diabetic retinopathy among a diverse group of individuals with DM enrolled in a large managed-care network. By following beneficiaries longitudinally, we sought to confirm previously identified risk factors and to define additional risk factors that may be associated with progression from NPDR to PDR. Finally, using the risk factors identified from our regression models, we developed a risk score that clinicians can use to identify groups of individuals who are at low and high risk of retinopathy progression.

RESEARCH DESIGN AND METHODS

Data source
The i3 InVision Data Mart database (Ingenix, Eden Prairie, MN) contains detailed fully

deidentified records of all beneficiaries in a large managed-care network throughout the U.S. We had access to data for a subset of beneficiaries who had any form of eye care from 1 January 2001 through 31 December 2009. This subset consisted of beneficiaries who had one or more ICD-9, Clinical Modification (ICD-9-CM) (14), codes for any eye-related diagnosis (360–379.9) or Current Procedural Terminology-4 (15) code for any eye-related visits, diagnostic or therapeutic procedures (65091–68899 or 92002–92499), or any other claims submitted by an ophthalmologist or optometrist during their time in the medical plan. For each beneficiary, we had access to all medical claims (inpatient, outpatient, and skilled nursing facility) for ocular and nonocular conditions along with sociodemographic information (age, sex, race, education level, and household net worth) for each enrollee. The database also contains all outpatient medication prescriptions along with all available outpatient laboratory test results for each enrollee during their time in the plan. All patients who were enrolled in the medical plan were also fully enrolled in the pharmacy plan. This database has previously been used to study other ophthalmologic conditions including glaucoma and age-related macular degeneration (16,17).

Patients

All individuals age ≥30 years who were in the database continuously and had two or more diagnoses of DM based on ICD-9-CM billing codes 250.xx were identified. Continuous enrollment in the plan is uninterrupted plan enrollment from the date of plan enrollment. Next, we required each beneficiary to have one visit or more to an eye care provider (ophthalmologist or optometrist) during their first year in the plan with no diagnosis of NPDR or PDR (to help exclude nonincident cases). We then identified a subset of enrollees who were newly diagnosed with NPDR (ICD-9-CM codes 362.01, 362.03, 362.04, 362.05, and 362.06) after their first year in the medical plan. Patients were followed from their index date (i.e., the date when they were first diagnosed with NPDR) for determination of whether they went on to develop PDR. We also required all eligible enrollees to have one or more records of HbA_{1c} after their index date for assessment of the impact of glycemic control on retinopathy progression and one or more visits to an eye care provider after the index date for

determination of whether progression to PDR occurred. Individuals in the plan for <1 year and beneficiaries who were not in the plan continuously were excluded. In addition, individuals who had any record of PDR (ICD-9-CM code 362.02) prior to the index date were excluded.

Diagnosis of NPDR and PDR

Among those who were diagnosed with NPDR, 4,330 of 4,617 (94%) diagnoses were made by eye care providers. A recent study comparing the accuracy of billing records for PDR with information listed in actual medical records found that 94% of patients seen by eye care providers who received a billing code for PDR had evidence of the condition in the medical record (18).

Analyses

Statistical analyses were performed using SAS, version 9.2 (SAS, Cary, NC). Participant characteristics were summarized for those with NPDR who did and did not develop PDR using means and SDs for continuous variables and frequencies and percentages for categorical variables.

Multivariable Cox regression

A multivariable Cox proportional hazard regression analysis was performed to determine the factors that affected the progression from NPDR to PDR. The proportional hazard assumption was tested by checking interactions between each of the key predictor variables and time and was not found to be violated (19). A delayed entry model was used where individuals were followed from the index date (the day they first were diagnosed with NPDR) to the day they had their last visit to an eye care provider. In the model, we assessed the association between the following factors and risk of diabetic retinopathy progression: age at first diagnosis of NPDR, sex, race, comorbid hypertension, dyslipidemia, diabetic nephropathy, diabetic neuropathy, nonhealing ulcers, HbA_{1c} level, and treatment with ACE inhibitors, statins, sulfonylureas, metformin, and insulin. In the regression model, HbA_{1c} level was treated as a time-dependent covariate, meaning HbA_{1c} level was updated each time a new measurement was taken. In addition, each medication class was treated as time-dependent covariates in the model. For each class, we summed the total number of days used in the year prior to the index date. Then, each day after the index date that the enrollee continued to be followed

in the plan, we summed the total days' supply of each medication consumed within the past year. In the regression model, we assessed the effect of daily use of medications in the past year. The regression model output was converted to monthly use for ease of interpretation. While our data source lacked information on actual blood pressure readings, we were able to classify each enrollee as being normotensive (no record of hypertension), having "uncomplicated" hypertension, or having "complicated" hypertension. We defined uncomplicated hypertension as no evidence of end-organ damage from hypertension, while enrollees with complicated hypertension had at least one record of end organ damage from hypertension (e.g., hypertensive nephropathy, retinopathy). The regression models generated hazard ratios (HRs) with 95% CIs. Tests for multicolinearity were performed using the variance inflation factor test, and there was no strong correlation among any of the variables in the model (variance inflation factor <5 for all comparisons). Since the use of time-dependent covariates for predictive purposes is controversial (20), as a sensitivity analysis we reran our model replacing each of the time-dependent covariates with time-constant variables to determine whether that would impact the study findings. The regression model was validated using hold-out cross-validation, with a 50% training sample and a 50% testing sample.

Using the findings from the Cox regression model, we determined the 3- and 5-year probability of progressing from NPDR to PDR for patients with different levels of risk factors. In addition, we created plots depicting how the risk of experiencing retinopathy progression varied based on different levels of specific risk factors. For all analyses, $P < 0.05$ was considered statistically significant. The University of Michigan Institutional Review Board determined that this study was exempt from human subjects' approval, as the data had been completely deidentified before being provided to the researchers.

RESULTS—A total of 4,617 beneficiaries with NPDR were eligible for the study. Of those eligible, 307 (6.7%) progressed from NPDR to PDR. The median length of time enrollees were followed from the index date was 1.7 years. Those with NPDR who did not develop PDR were in the plan for a median of 1.7 years, and those with NPDR who progressed to PDR were in the plan for a median of 1.1

years ($P < 0.0001$) from the index date. Individuals with NPDR who did not develop PDR had an average of 7.0 visits to eye care providers, while those who experienced progression from NPDR to PDR had an average of 10.0 eye care provider visits ($P < 0.0001$).

The median age for those with NPDR who did not progress to PDR was 59.5 years and for those with NPDR who progressed to PDR was 57.3 years ($P = 0.0005$) There was no significant difference in the proportion of individuals of different races or the proportion of males and females who did or did not progress to PDR ($P > 0.2$ for both comparisons). Among enrollees with NPDR who did not progress to PDR, 7.3% had no record of hypertension, 63.4% had uncomplicated hypertension, and 29.4% had hypertension complicated by end-organ damage.

By comparison, among those with NPDR who progressed to PDR, 5.5% had no record of hypertension, 57.3% had uncomplicated hypertension, and 37.1% had complicated hypertension. A greater proportion of those who experienced progression from NPDR to PDR had diabetic nephropathy (39.1 vs. 26.0%), diabetic neuropathy (50.5 vs. 36.8%), and nonhealing foot ulcers (19.9 vs. 11.4%) relative to those with NPDR who did not progress to PDR ($P < 0.05$ for all comparisons) (Table 1).

Multivariable Cox regression
After adjustment for age, sex, race, medical conditions, and medications, every 1-point increase in HbA_{1c} level was associated with a 14% increase in the hazard of progressing from NPDR to PDR (adjusted HR 1.14 [95% CI 1.07–1.21]).

For example, a rise in HbA_{1c} from 8.0 to 10.0% was associated with a 28% increased risk of progression from NPDR to PDR. The presence of comorbid diabetic nephropathy increased the hazard of progression from NPDR to PDR by 29% (1.29 [0.99–1.67]), a finding of marginal statistical significance ($P = 0.06$). The presence of comorbid nonhealing foot ulcers increased the hazard of progression from NPDR to PDR by 54% (1.54 [1.15–2.07]). Factors that were not found to be associated with progression from NPDR to PDR included age, sex, race, comorbid dyslipidemia, hypertension, and diabetic neuropathy or the use of statins, ACE inhibitors, or any of the classes of antihyperglycemic medications included in the model (Table 2). In a sensitivity analysis, we explored whether adding an additional class of antihypertension medications (angiotensin receptor blockers) affected the results. The class of medications was not found to be associated with an increased or decreased risk of retinopathy progression, and its inclusion in the model did not appreciably affect the findings of other variables tested. In a second sensitivity analysis, we replaced each of the time-dependent covariates (medication use and HbA_{1c}) with time-constant variables, and HbA_{1c} and nonhealing ulcers each continued to be associated with retinopathy progression (results not shown).

Progression probabilities
Based on the Cox regression models, we estimated the probability of progressing from NPDR to PDR based on the predictor variables listed above. The Supplementary Data depicts the equation to calculate survival probability. The estimated 3- and 5-year progression probability for a group of low-risk individuals (e.g., 80-year-old white females with HbA_{1c} levels of 6.0% who had uncomplicated hypertension and dyslipidemia; who had no diabetic nephropathy, neuropathy, or nonhealing ulcers present; and who take statins and metformin) was 3% (95% CI 1–5) and 5% (2–8), respectively. The estimated 3- and 5-year progression probability for a group of moderate-risk individuals (e.g., 60-year-old white females with HbA_{1c} levels of 12.0% who had uncomplicated hypertension and dyslipidemia, diabetic nephropathy, and no diabetic neuropathy or nonhealing ulcers and who took ACE inhibitors and metformin but no statins or other antihyperglycemics) was 11% (5–17) and 19% (8–18), respectively.

Table 1—*Characteristics of enrollees with NPDR who did and did not progress to PDR*

	No progression from NPDR to PDR	Progression from NPDR to PDR	Overall
Total	4,310 (93.3)	307 (6.7)	4,617
Time in plan (years)*	5.6 (2.1)	6.0 (2.1)	5.6 (2.1)
Age (years)*	59.2, 59.5 (9.9)	56.9, 57.3 (9.7)	59.1, 59.4 (9.9)
Sex			
Male	2,173 (50.4)	145 (47.2)	2,318 (50.2)
Female	2,137 (49.6)	162 (52.8)	2,299 (49.8)
Race			
White	3,233 (75.0)	224 (73.0)	3,457 (74.9)
Black	477 (11.1)	42 (13.7)	519 (11.2)
Latino	432 (10.0)	30 (9.8)	462 (10.0)
Asian	168 (3.9)	11 (3.6)	179 (3.9)
Household net worth (USD)			
<25,000	365 (8.5)	25 (8.1)	390 (8.5)
25,000–74,999	303 (7.0)	34 (11.1)	337 (7.3)
75,000–149,999	588 (13.6)	40 (13.0)	628 (13.6)
150,000–499,999	1,937 (44.9)	126 (41.0)	2,063 (44.7)
≥500,000	894 (20.7)	66 (21.5)	960 (20.8)
U.S. region of residence			
Northeast	759 (17.6)	44 (14.3)	803 (17.4)
Southeast	2,257 (52.4)	171 (55.7)	2,428 (52.6)
Midwest	1,039 (24.1)	78 (25.4)	1,117 (24.2)
West	254 (5.9)	14 (4.6)	268 (5.8)
Hypertension status*			
No hypertension	314 (7.3)	17 (5.5)	331 (7.2)
Hypertension without complications	2,731 (63.4)	176 (57.3)	2,907 (63.0)
Hypertension with complications	1,265 (29.4)	114 (37.1)	1,379 (37.1)
Dyslipidemia	4,108 (95.3)	292 (95.1)	4,400 (95.3)
Diabetic nephropathy*	1,122 (26.0)	120 (39.1)	1,242 (26.9)
Diabetic neuropathy*	1,587 (36.8)	155 (50.5)	1,742 (37.7)
Nonhealing ulcers*	490 (11.4)	61 (19.9)	551 (11.9)

Data are mean, median (SD); *N*; or *N* (%) unless otherwise indicated. *$P < 0.05$.

Table 2—*Cox regression models (univariable and multivariable)*

	Univariable regression	Multivariable regression
Age (years)	0.99 (0.98–1.00)	0.99 (0.98–1.01)
Sex		
Male	Ref.	Ref.
Female	1.12 (0.90–1.41)	1.11 (0.88–1.40)
Race		
White	Ref.	Ref.
Black	**1.41 (1.01–1.96)**	1.29 (0.92–1.82)
Latino	1.12 (0.77–1.65)	1.12 (0.76–1.65)
Asian American	1.08 (0.59–1.98)	1.35 (0.73–2.49)
Medical conditions		
Uncomplicated hypertension*	1.15 (0.69–1.92)	1.10 (0.64–1.88)
Complicated hypertension*	1.49 (0.88–2.51)	1.22 (0.69–2.15)
Dyslipidemia	0.81 (0.46–1.41)	0.83 (0.47–1.47)
Diabetic nephropathy	**1.57 (1.25–1.98)**	1.29 (0.99–1.67)
Diabetic neuropathy	**1.46 (1.16–1.83)**	1.15 (0.90–1.47)
Nonhealing ulcers	**1.84 (1.39–2.43)**	**1.54 (1.15–2.07)**
HbA_{1c}	**1.18 (1.12–1.25)**	**1.14 (1.07–1.21)**
Medications†		
ACE inhibitors	1.09 (0.83–1.44)	1.15 (0.85–1.55)
Statins	0.84 (0.63–1.13)	0.91 (0.66–1.26)
Sulfonylureas	0.76 (0.53–1.10)	1.04 (0.68–1.59)
Metformin	**0.63 (0.44–0.89)**	0.74 (0.49–1.11)
Insulin	**2.05 (1.42–2.96)**	1.45 (0.94–2.24)

Data are HR (95% CI). Boldface type indicates significance at $P < 0.05$. *Reference group (persons with no hypertension). †Medication use is reported as increased or decreased hazard for every additional year of use. For example, an HR of 0.91 for statins means that for every additional year of statin use, the hazard of experiencing retinopathy progression decreases by 9%.

The estimated 3- and 5-year progression probability for a group of very high-risk individuals (e.g., 40-year-old white females with HbA_{1c} levels of 12.0% who had uncomplicated hypertension, dyslipidemia, and diabetic nephropathy but no diabetic neuropathy or nonhealing ulcers present and were taking insulin, sulfonylureas, and ACE inhibitors but no statins or metformin) was 24% (8–38) and 38% (14–55), respectively. Figs. 1 and 2 depict the estimated progression probabilities over time for individuals with NPDR, varying selected risk factors in the model.

CONCLUSIONS—In this analysis involving 4,617 individuals with newly diagnosed NPDR, we identified three risk factors that are independently associated with progression to PDR: HbA_{1c} level, diabetic nephropathy, and comorbid nonhealing foot ulcers. Using data generated from the multivariable regression analyses, we developed a risk score for diabetic retinopathy progression. Data on the model parameters were used to identify a patient's 3- and 5-year risks of progressing to PDR. The 5-year risk of progression is as low as 5% for patients with few risk factors and as high as 38% for those with multiple factors.

Several longitudinal studies have analyzed the natural history of diabetic retinopathy. In the Blue Mountains Eye Study, the 5-year risk for progression to PDR among 139 persons with NPDR at baseline was 4.1% (21). Roy and Affouf reported that among 725 black patients with insulin-dependent DM, 15% progressed to PDR from no retinopathy or NPDR over 6 years (22). Vitale et al. reported that 9.2% of 269 patients with mild NPDR progressed to PDR over 8 years (23). Among 703 UKPDS participants with retinopathy present at diagnosis, 29% experienced a two-step worsening of their retinopathy on the Early Treatment of Diabetic Retinopathy Study scale over 6 years (4). The WESDR described a 37% incidence of progression to PDR in a population of type 1 diabetic patients without retinopathy or with NPDR over 14 years (9). A meta-analysis of 28 studies by Wong et al., in which 55% entered the study without diabetic retinopathy, demonstrated a pooled incidence of PDR of 11% over 4 years (24). In our analysis, the proportion of persons with NPDR

who progressed to PDR was 6.7%. Comparisons of these population-based observational studies with one another and with the findings of our analysis are difficult because of differences in the types of eye care providers monitoring the study participants, the method of detecting disease progression (dilated ophthalmoscopy vs. retinal photographs vs. claims data), the length of follow-up, the level of baseline retinopathy, the number of examinations in the follow-up period, and the sociodemographic characteristics of the sample. Despite the differences in study methodology, the proportion exhibiting progression in our study is similar to those of the population-based studies.

Many studies have demonstrated an association between level of glycemic control and progression of diabetic retinopathy (4,22,23,25,26). After adjustment in our analysis for potential confounding factors, every additional 1-point increase in HbA_{1c} level was associated with a 14% increased risk for progression to PDR. Systemic hypertension (9,22) and renal disease (22,26) are risk factors associated with progression to PDR observed in some, but not all (23), studies. We observed a marginally increased risk of progression in those with comorbid nephropathy ($P = 0.06$) and no association between systemic hypertension and progression to PDR. Other previously reported factors associated with retinopathy progression include younger age at DM diagnosis (25), longer time since DM diagnosis (25), male sex (4), baseline total caloric intake (27), low diastolic blood pressure (25), higher waist-to-hip ratio (25), larger retinal venular diameter (28), and PDR in the contralateral eye (26). We found no association between age, sex, or race and risk for disease progression (for each, $P > 0.05$); some other potential risk factors—notably, DM duration—could not be assessed using administrative claims data.

We considered that nonhealing foot ulcers might contribute to retinopathy progression after observing patients in our clinics with both of these conditions. Studying 3,719 persons with DM, Leese et al. previously found increased odds for foot ulcers in patients with mild-to-moderate NPDR compared with odds in those who had no retinopathy; compared with odds in patients who had mild-to-moderate NPDR, the odds were even higher among those with severe NPDR (29). In 2005, the French Working Group on the Diabetic Foot found that comorbid retinopathy was associated
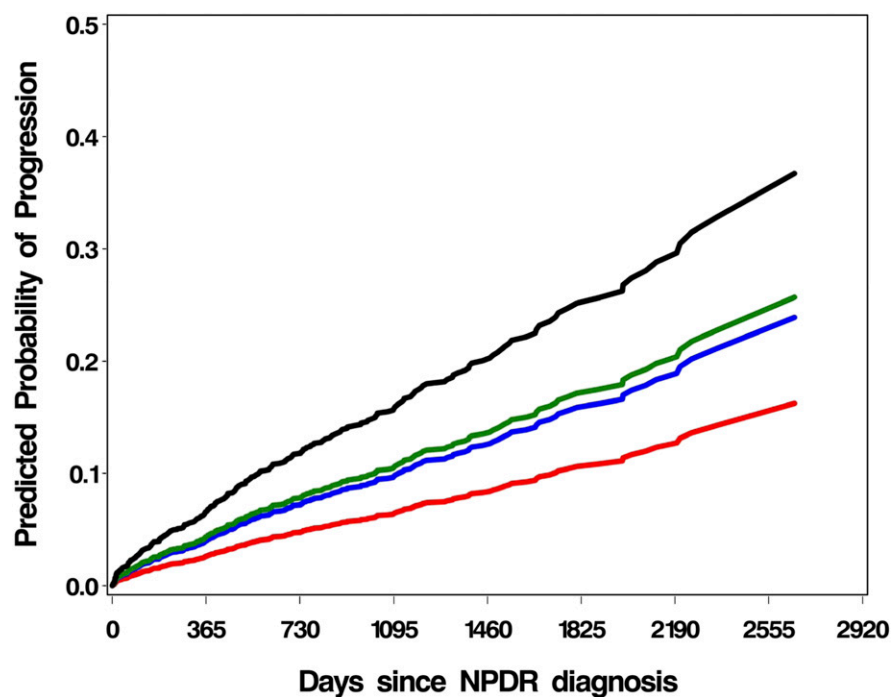
Figure 1—*Impact of HbA$_{1c}$ and nonhealing ulcers on risk of progression of diabetic retinopathy. Red, HbA$_{1c}$ of 8 patients with no nonhealing ulcers; blue, HbA$_{1c}$ of 8 with nonhealing ulcers; green, HbA$_{1c}$ of 12 with no nonhealing ulcers; black, HbA$_{1c}$ of 12 with nonhealing ulcers. For all groups, age = 60 years, no nephropathy; all other variables at average levels.*

with a fourfold increased odds of being at high risk for foot ulcers (30). Nonhealing ulcers often lead to amputation. Moss et al. found the incidence of lower-extremity amputation to be higher among patients with PDR than among those without retinopathy (31–33). In a 7-year follow-up of 733 patients with DM by Hämäläinen et al., those with new amputations were more likely to have diabetic retinopathy (34). Pima Indians with lower-extremity amputations had a fivefold increased risk for NPDR and a 21-fold increased risk for PDR compared with control participants with DM but no lower-extremity amputations (35). Our analysis, with adjustment for potential confounding factors, indicates a 54% increased hazard for progression from NPDR to PDR in patients with nonhealing ulcers.

Several possible mechanisms may explain this increased risk. First, nonhealing foot ulcers are associated with elevated levels of circulating cytokines, such as tumor necrosis factor-α (36) and interleukin-1β (37,38), and these factors are associated with elevated risk for retinopathy (39). Second, advanced glycation end products also contribute to the inflammatory response of DM and play a role in the development of diabetic retinopathy and impaired wound healing (38,40,41).

Third, levels of proinflammatory macrophages increase in persons with foot ulcers and diabetic retinopathy (42). Thus, the presence of nonhealing diabetic ulcers may indicate elevated systemic levels of inflammatory mediators, advanced glycation end products, and macrophages that, when present in the retina, cause a cascade of events resulting in PDR.

If confirmed, the association between nonhealing ulcers and retinopathy progression could have important implications for clinical practice. Control of nonhealing ulcers may help to reduce progression of NPDR to PDR, the risk of vision loss, and the need for laser surgery. Moreover, improved communication with podiatrists may allow eye care providers to be better aware of patients with DM who would benefit from close monitoring for worsening retinopathy.

Risk scores can be useful tools for identifying persons at low, moderate, and high risk for an outcome of interest. In ophthalmology, the Ocular Hypertension Treatment Study investigators developed a risk calculator to help clinicians determine the likelihood of glaucoma in patients with ocular hypertension (13). Risk calculators aid decision making on the frequency and intensity of patient monitoring and can serve as tools to educate

patients. For example, a clinician could inform a patient of her 5-year risk for retinopathy progression, according to the calculated risk score, and then alter the value of modifiable risk factors, such as the HbA$_{1c}$ level, to demonstrate the potential impact of improved or worsened glucose control on her risk for blindness.

We know of only one other diabetic retinopathy risk score. Aspelund et al. designed an algorithm to determine the appropriate screening interval on the basis of a patient's risk for macular edema or PDR. Prevalence data from the Icelandic eye-screening database and known risk factors from the WESDR and UKPDS were incorporated into the model, which gives a suggested interval between ophthalmic examinations according to DM duration, HbA$_{1c}$ level, blood pressure, and the presence and grade of existing retinopathy (43). By contrast, our calculator specifically predicts the likelihood of progressing from NPDR to vision-threatening PDR on the basis of sociodemographic data and nonocular comorbidities and includes the novel contribution of nonhealing ulcers.

Study strengths and limitations

A major strength of this study is its large size. Many patients with NPDR were followed longitudinally over time to determine who developed PDR. Unlike many population-based studies that rely on a single local community for patient recruitment, our analysis involves a diverse group of U.S. patients with DM. Our models are adjusted for potential confounding variables, including sociodemographic characteristics, comorbid medical conditions, and use of selected medications.

This study also has several limitations. We cannot know for certain whether particular risk factors are causing retinopathy progression or merely represent markers of disease progression. Second, results of our analysis, involving U.S. health insurance carriers, may not be generalizable to uninsured and non-U.S. populations. Third, because health care claims databases contain no information on clinical parameters, potential factors such as disease duration, blood pressure, BMI, and tobacco use went unexamined. Also excluded from our analysis was patients' baseline severity of NPDR, as ICD-9-CM billing codes lack such details. At baseline, some patients may have had mild NPDR, with few microaneurysms, whereas others may have had severe NPDR. Finally, additional research should be conducted to validate our
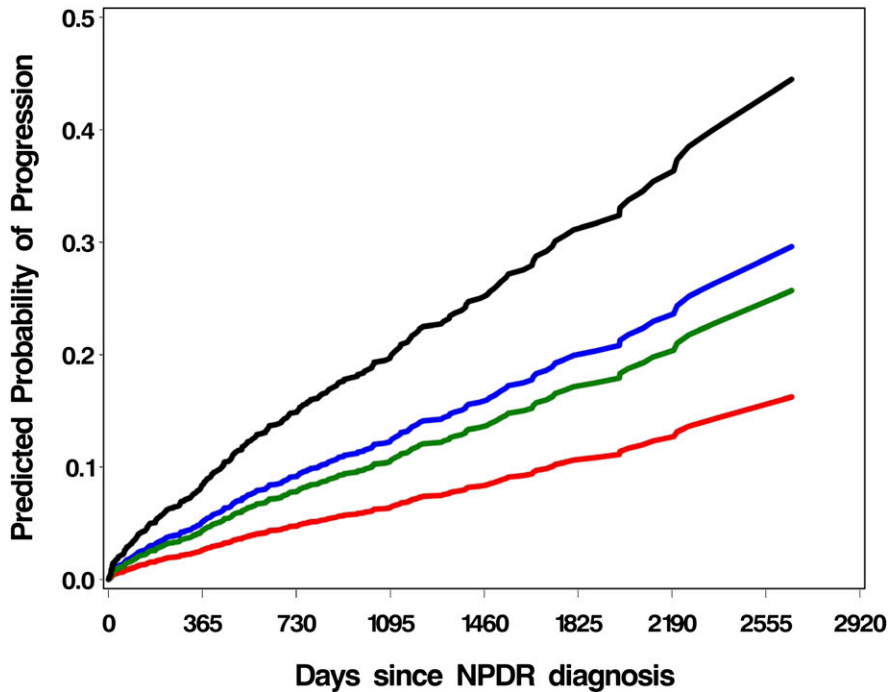
Figure 2—*Impact of HbA$_{1c}$, nephropathy, and nonhealing ulcers on risk of progression of diabetic retinopathy. Red, HbA$_{1c}$ of 8 patients with no nephropathy or nonhealing ulcers; blue, HbA$_{1c}$ of 8 with nephropathy and nonhealing ulcers; green, HbA$_{1c}$ of 12 with no nephropathy or nonhealing ulcers; black, HbA$_{1c}$ of 12 with nephropathy and nonhealing ulcers. For all groups, age = 60 years and average levels of other variables are presented.*

findings, prospectively demonstrating the influence of these and other factors, before providers rely on the risk calculator in clinical practice.

In conclusion, we have identified several factors associated with progression from NPDR to PDR, including HbA$_{1c}$ level, diabetic nephropathy, and nonhealing foot ulcers. On the basis of our regression model, we developed a risk score that can aid in identifying groups of patients at low, moderate, and high risk for progression over 5 years. Once validated, this risk score may assist eye care providers in making clinical decisions, such as the frequency of monitoring in patients with NPDR. The model can also be adapted to include other variables as new questions about the risks of DM complications arise.

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