Predictors of Lost to Follow-Up in Patients Being Treated for Proliferative Diabetic Retinopathy

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• PURPOSE: **To identify risk factors for patients with proliferative diabetic retinopathy (PDR) who are lost to follow-up (LTFU) while undergoing intravitreal injections of anti-VEGF (IVIs) and/or panretinal photocoagulation (PRP) at an urban institution.**

• DESIGN: **Retrospective cohort study.**

• METHODS: **A chart review was performed in a total of 418 adult patients with PDR who received IVI and/or PRP between January 1, 2014, and June 1, 2018, at the authors' institution. Rates of LTFU, risk factors associated with LTFU, and vision outcomes were assessed.**

• RESULTS: **Of a total of 418 patients, 256 patients (61%) were LTFU. Risk factors positively associated with LTFU on multivariate analysis included non-English as the primary language (odds ratio [OR], 1.83; $P = .006$); age 56-65 years old (OR, 1.86; $P = .014$); age older than 65 years (OR, 1.94; $P = .027$) compared to age 55 years or younger; living 20 miles or less from the institution (OR, 2.68; $P = .009$); having greater than 5 comorbidities (OR, 2.38; $P = .034$); seeing 20 or more distinct departments (OR, 4.66; $P = .007$); missing more than 10% of non-eye care appointments (OR, 1.61; $P = .038$); and receiving only PRP compared to only IVIs (OR, 1.93; $P = .031$).**

• CONCLUSIONS: **A high percentage of patients treated for PDR at the authors' institution were LTFU over a 4-year time span. Identifying patients at high risk for being LTFU may help in choosing treatment modality and appropriate patient counseling. (Am J Ophthalmol 2020;216:18–27. Published by Elsevier Inc.)**

DIABETIC RETINOPATHY (DR) IS A LEADING CAUSE of blindness among working aged adults in developed countries. Historically, panretinal photocoagulation (PRP) has been the mainstay of treatment for proliferative diabetic retinopathy (PDR). However, the advent of intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents (IVI) has significantly altered the management of vision-threatening DR and other ischemic retinal vascular diseases. The Diabetic Retinopathy Clinical Research (DRCR) Network protocol S showed noninferiority of ranibizumab monotherapy compared to PRP for active PDR,[1] whereas the UK-based CLARITY trial showed that treatment with aflibercept resulted in superior visual outcomes compared to PRP.[2] However, recent studies indicate that outcomes in landmark trials are often not matched in the clinical environment. Holekamp and associates[3] showed that real-world patients with diabetic macular edema receive fewer IVIs, resulting in inferior visual outcomes compared to those in clinical trials. Similar findings have been demonstrated in the treatment of neovascular age-related macular degeneration[4] and retinal vein occlusions.[5] These studies suggest that inadequate follow-up may contribute to suboptimal treatment patterns.

As a chronic disease, PDR requires frequent, long-term in-office treatments, making patient adherence to scheduled follow-up appointments critical to improving visual outcomes. In the DRCR Network protocol S,[6] only 66% of treated PDR patients completed 5 years of follow-up, highlighting the issue of patient adherence even in the "ideal" clinical trial setting. Recent "real world" studies[7,8] have identified risk factors for patients who are lost to follow-up (LTFU), who are being treated for PDR, including younger patients, non-white patients, those of lower incomes, those who lack mobility, and those who need assistance with transportation. In addition, diabetic patients, especially those who have reached the advanced stage of PDR, often have multiple comorbid medical issues[9] that may impact their ability to follow treatment scheduling recommendations. Furthermore, recent data suggest that, in patients with PDR who are LTFU, those treated with IVIs may have worse clinical outcomes than those treated with PRP.[10] As such, identification of patients who may have difficulty adhering to treatment is pivotal in optimizing the management of this disease.

Several previous studies have identified the low-income and minority patient populations served by safety-net hospitals as particularly affected by poor adherence to treatment recommendations in the management of DR. Only 55% of patients surveyed at a Los Angeles safety net clinic in 2014 had received DR screening during the previous year.[11] Even successful efforts at early disease identification through telemedicine are limited by patient adherence barriers. Keenum and associates[12] reported that, although almost 85% of patients served by a government-funded

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Alabama health system received nonmydriatic fundus photo screening, less than 30% of patients adhered to the recommended ophthalmic follow-up, and over 50% had had no documented eye care appointment within 2 years of screening.

The authors' institution is the largest safety-net hospital in New England, caring for many patients from underserved populations who, based on risk factors identified in previous studies, may be at increased risk for being LTFU. This study investigated the rate of LTFU amongst patients who were being treated with IVI and/or PRP for PDR at a safety-net hospital and evaluated a more extensive list of possible predictors of LTFU than previously published. For the purposes of this study, LTFU was defined as the failure to return to care for at least 6 months after an appointment with a vitreoretinal specialist.

SUBJECTS AND METHODS

• **STUDY POPULATION:** Approval from the Boston Medical Center Institutional Review Board was obtained prior to conducting this study, which was performed in accordance with the Health Insurance Portability and Accountability Act of 1996. Patients were identified for retrospective chart review using International Classifications of Diseases 9th and 10th revision codes for PDR and Current Procedural Terminology billing codes for IVI and PRP. Selection criteria for the study included males and females 18 years of age and older with a diagnosis of PDR who received IVI and/or underwent PRP at the authors' institution between January 1, 2014, and June 1, 2018. Patients were excluded from the study if they did not have at least 1 follow-up visit before June 1, 2018 that was documented at least 6 months after initial intervention. Patients were included only if they had at least 2 visits within the study period, including 1 visit at least 6 months after the intervention with PRP or IVI. Patients could be included in the study if they had IVI or PRP prior to the study period but were required to have at least 1 intervention with at least 6 months' follow-up during the study period. Overall, a total of 418 patients qualified for inclusion in the study.

• **DEFINITION OF LOST TO FOLLOW-UP:** The intervals between visits with a vitreoretinal specialist were assessed. The main outcome of this study was LTFU, which was defined as at least 1 interval between follow-up appointments exceeding a duration of 6 months (180 days), where the last documentation prior to LTFU recommended a follow-up of less than 6 months. If recommended follow-up was 6 months or greater, LTFU was defined as a failure to return to the clinic for 20 days or more past the recommended follow-up time. For example, a patient with a recommended follow-up time of 8 months, or 240 days, was considered LTFU if they did not return for care in 260 days or more. The 20-day cutoff was instituted at the investigators' discretion to avoid short and likely clinically insignificant delays (usually caused by clinic scheduling issues as opposed to patient adherence) from overestimating the rate of being LTFU. Subjects who were LTFU for more than 6 months multiple times during the study period were only counted as a single data point.

• **VISIT SCHEDULING:** Telephone or in-person interpreters were used at all visits where language differences might present a barrier to effective communication of treatment and follow-up recommendations. At the conclusion of every clinic visit, all patients were given a written schedule documenting the date, time, and location of their next appointment. All patients with appointments booked more than 3 weeks in advance were sent a reminder letter in their preferred language to arrive 1 week prior to their scheduled appointment. In addition, text message or phone call reminders were sent to all patients within 3 days of their scheduled appointment. Patients missing a scheduled follow-up appointment were sent a reminder postcard within 1 month of their missed visit with instructions to call to reschedule.

• **PATIENT CHARACTERISTICS:** A variety of patient characteristics were collected from the electronic medical record (EMR) for the study. Demographic factors included sex, race, ethnicity, primary language, and age. Social factors included history of psychiatric illness, substance abuse disorder, homelessness or food pantry visits, and a documented history of noncompliance. History of noncompliance was defined as 1 or more instances of clinical documentation (in any medical specialty) of the following terms: "noncompliance," "noncompliant," "nonadherence," "nonadherent," "not compliant," and "not adherent." Economic factors included type of insurance on file, distance between home zip code and clinic, and weighted (by household size) average household income (AHI) by zip code as published by the US Census Bureau.[13,14] To determine distance to the clinic, Google Maps (Google Inc., Mountain View, California) was used to measure the straight line distance between the clinic and the central location of each zip code. Hospital factors included whether the patient had a primary care provider on file, whether they had a primary care provider that was on staff at the authors' institution, total number of comorbidities (as defined by Sundararajan and associates[15]) in the patient's problem list, number of distinct departments in which the patient had been seen during the study period, number of inpatient and observation unit admissions during the study period, number of emergency department (ED) visits during the study period, and percentage of all non-eye care visits for which the patient did not show or cancelled during the study period (non-eye care missed appointment rate). Clinical factors

TABLE 1. Characteristics of Patients with PDR by LTFU Status

Variable	Categories	Followed Up (n = 162)	LTFU (n = 256)	Total (N = 418)
Sex	Male	89 (37.4%)	149 (62.6%)	238
	Female	73 (40.6%)	107 (59.4%)	180
Race	White	29 (46.8%)	33 (53.2%)	62
	Black	71 (36.6%)	123 (63.4%)	194
	Other	7 (46.7%)	8 (53.3%)	15
	Unreported	55 (37.4%)	92 (62.6%)	147
Hispanic/Latino	No	112 (39.6%)	171 (60.4%)	283
	Yes	50 (37.0%)	85 (63.0%)	135
Primary Language	English	91 (43.5%)	118 (56.5%)	209
	Non-English	71 (34.0%)	138 (66.0%)	209
Age	≤55	86 (46.5%)	99 (53.5%)	185
	56-65	46 (32.9%)	94 (67.1%)	140
	>65	30 (32.3%)	63 (67.7%)	93
Psychiatric history	No	95 (41.1%)	136 (58.9%)	231
	Yes	67 (35.8%)	120 (64.2%)	187
Substance abuse history	No	145 (38.0%)	237 (62.0%)	382
	Yes	17 (47.2%)	19 (52.8%)	36
History of homelessness	No	158 (39.2%)	245 (60.8%)	403
	Yes	4 (26.7%)	11 (73.3%)	15
Food pantry visits	No	152 (39.5%)	233 (60.5%)	385
	Yes	10 (30.3%)	23 (69.7%)	33
History of noncompliance	No	102 (44.2%)	129 (55.8%)	231
	Yes	60 (32.1%)	127 (67.9%)	187
Insurance type	Commercial	20 (31.7%)	43 (68.3%)	63
	Medicare	26 (28.0%)	67 (72.0%)	93
	Medicaid	70 (42.4%)	95 (57.6%)	165
	Free Care	4 (33.3%)	8 (66.7%)	12
	Unreported	42 (49.4%)	43 (50.6%)	85
Distance from institution	>20	25 (61.0%)	16 (39.0%)	41
	≤20	137 (36.3%)	240 (63.7%)	377
Average household income	>$80,000	31 (42.5%)	42 (57.5%)	73
	$40,000-$80,000	104 (37.1%)	176 (62.9%)	280
	<$40,000	27 (41.5%)	38 (58.5%)	65
PCP on file	No	24 (48.0%)	26 (52.0%)	50
	Yes	138 (37.5%)	230 (62.5%)	368
PCP at same institution	No	35 (49.3%)	36 (50.7%)	71
	Yes	127 (36.6%)	220 (63.4%)	347
Number of comorbidities	≤5	152 (41.4%)	215 (58.6%)	367
	>5	10 (19.6%)	41 (80.4%)	51
Number of departments seen	<20	158 (40.9%)	228 (59.1%)	386
	≥20	4 (12.5%)	28 (87.5%)	32
Inpatient/observation admissions	≤2	131 (42.0%)	181 (58.0%)	312
	>2	31 (29.2%)	75 (70.8%)	106
Number of ED visits	0	78 (40.4%)	115 (59.6%)	193
	1-5	74 (37.9%)	121 (62.1%)	195
	>5	10 (33.3%)	20 (66.7%)	30
Non-eye care missed appointment rate	≤10%	78 (42.6%)	105 (57.4%)	183
	>10%	74 (35.1%)	137 (64.9%)	211
	No Data	10 (41.7%)	14 (58.3%)	24
First HbA1c	<6.5	10 (31.3%)	22 (68.8%)	32
	6.5-7.9	36 (43.4%)	47 (56.6%)	83
	8-9.9	47 (36.7%)	81 (63.3%)	128
	≥10	49 (38.3%)	79 (61.7%)	128
	Unreported	20 (42.6%)	27 (57.4%)	47

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TABLE 1. Characteristics of Patients with PDR by LTFU Status (*Continued*)

Variable	Categories	Followed Up (n = 162)	LTFU (n = 256)	Total (N = 418)
Diabetes type	Type 1	11 (36.7%)	19 (63.3%)	30
	Type 2	151 (38.9%)	237 (61.1%)	388
History of vitreous hemorrhage	No	39 (36.4%)	68 (63.6%)	107
	Yes	123 (39.5%)	188 (60.5%)	311
History of NVI/NVG	No	114 (35.8%)	204 (64.2%)	318
	Yes	48 (48.0%)	52 (52.0%)	100
Treatment modality	IVI	56 (43.1%)	74 (56.9%)	130
	PRP	33 (31.4%)	72 (68.6%)	105
	Both	73 (39.9%)	110 (60.1%)	183
Longest recommended follow-up time	≤6 Months	160 (39.8%)	242 (60.2%)	402
	>6 Months	8 (50.0%)	8 (50.0%)	16
Best initial visual acuity	≥20/40	103 (35.5%)	187 (64.5%)	290
	20/50-20/200	52 (45.6%)	62 (54.4%)	114
	<20/200	7 (50.0%)	7 (50.0%)	14
Best final visual acuity	≥20/40	95 (34.6%)	180 (65.4%)	275
	20/50-20/200	57 (49.6%)	58 (50.4%)	115
	<20/200	10 (35.7%)	18 (64.3%)	28
Change in visual acuity	Worsened	33 (35.5%)	60 (64.5%)	93
	Improved	29 (42.7%)	39 (57.3%)	68
	No Change	100 (38.9%)	157 (61.1%)	257

ED = emergency department; NVI = neovascularization of the iris; HbA1c = hemoglobin A1c; IVI = intravitreal injection; LTFU = lost to follow-up; NVG = neovascular glaucoma; PCP = primary care physician; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation.

included the earliest recorded hemoglobin A1c (HbA1c) level during the study window, diabetes type, history of vitreous hemorrhage, history of neovascularization of the iris (NVI) or neovascular glaucoma (NVG), PDR treatment modality administered during the study window (PRP alone, IVIs alone, or both), and length of longest recommended follow-up time. Finally, visual acuity data including best initial visual acuity (BIVA), best final visual acuity (BFVA), and change in visual acuity were collected. BFVA was defined as VA in the better seeing eye in patients with bilateral PDR at the final vitreoretinal appointment during the study window. If only 1 eye had PDR at the final visit, the VA of that eye was used. Best initial visual acuity (BIVA) was defined as VA in the better seeing eye at the initial vitreoretinal appointment regardless of whether that eye had PDR or not. To determine changes in VA, VA data at the initial and final vitreoretinal appointments were converted to the logarithm of the minimum angle of resolution (logMAR) and the difference between these two values was calculated. A change in VA of 2 lines or greater was considered significant.

• **STATISTICAL ANALYSIS:** Statistical analysis was performed using SPSS version 25 software (IBM, Armonk, NY). Continuous variables were categorized based on groupings used previously in medical literature, clinical relevance, or based on distribution. Univariate logistic regression was used to determine significant differences in rates of LTFU based on variables extracted from the EMR detailed above. A stepwise backward likelihood multivariate logistic regression was then performed, including variables with P values <.2 on univariate global test or those with P values <.2 for any variable subcategory on univariate analysis for variables with greater than 2 categories. P values of <.05 were considered statistically significant on univariate and multivariate regression.

RESULTS

A TOTAL OF 418 PATIENTS QUALIFIED FOR INCLUSION IN THE study, of which 256 patients (61%) were LTFU. Of patients who were LTFU, mean time of LTFU was 344 days (range, 181-1,078 days), with a median of 273 days. The mean (±SD) recommended follow-up time for visits prior to being LTFU was 3.3 (±2.1) months. Sixteen patients (3.83%) had a recommended follow-up time of greater than 6 months at least once during the study period. Descriptive characteristics of the authors' cohort are summarized in Table 1. Among all patients, 130 patients (31.10%) received IVIs alone during the study period compared to 105 patients (25.12%) who received PRP

TABLE 2. Univariate and Multivariate Logistic Regression Models for Predictors of LTFU in Patients Treated for PDR

		Univariate Model		Multivariate Model	
Variable	Categories	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Sex	Male	Reference		-	-
	Female	0.88 (0.59-1.30)	.511	-	-
Race	White	Reference		-	-
	Black	1.52 (0.85-2.71)	.154	-	-
	Other	1.00 (0.32-3.11)	.994	-	-
	Unreported	1.47 (0.81-2.68)	.209	-	-
Hispanic/Latino	No	Reference		-	-
	Yes	1.11 (0.73-1.70)	.618	-	-
Primary language	English	Reference		Reference	-
	Non-English	1.50 (1.009-2.227)	.045[a]	1.83 (1.19-2.82)	.006[a]
Age	≤55	Reference		Reference	
	56-65	1.78 (1.13-2.80)	.014[a]	1.86 (1.13-3.05)	.014[a]
	>65	1.82 (1.08-3.08)	.024[a]	1.94 (1.08-3.48)	.027[a]
Psychiatric history	No	Reference		-	-
	Yes	1.25 (0.84-1.86)	.269	-	-
Substance abuse history	No	Reference		-	-
	Yes	0.68 (0.34-1.36)	.278	-	-
History of homelessness	No	Reference		-	-
	Yes	1.77 (0.55-5.67)	.334	-	-
Food pantry visits	No	Reference		-	-
	Yes	1.50 (0.70-3.24)	.302	-	-
History of noncompliance	No	Reference		-	-
	Yes	1.67 (1.2-2.50)	.012[a]	-	-
Insurance type	Commercial	Reference		-	-
	Medicare	1.12 (0.60-2.41)	.611	-	-
	Medicaid	0.63 (0.34-1.17)	.142	-	-
	Free Care	0.93 (0.25-3.46)	.914	-	-
	Unreported	0.48 (0.24-0.94)	.032[a]	-	-
Distance from institution	>20	Reference		Reference	
	≤ 20	2.74 (1.41-5.31)	.003[a]	2.68 (1.27-5.63)	.009[a]
Average household income	>$80,000	Reference		-	-
	$40,000-$80,000	1.25 (0.74-2.11)	.405	-	-
	<$40,000	1.04 (0.53-2.05)	.912	-	-
PCP on file	No	Reference		-	-
	Yes	1.54 (0.85-2.79)	.155	-	-
PCP at same institution	No	Reference		-	-
	Yes	1.68 (1.01-2.82)	.047[a]	-	-
Number of morbidities	≤ 5	Reference		Reference	
	>5	2.90 (1.41-5.97)	.004[a]	2.38 (1.07-5.29)	.034[a]
Number of departments seen	<20	Reference		Reference	
	≥20	4.85 (1.67-14.10)	.004[a]	4.66 (1.52-14.28)	.007[a]
Inpatient/observation admissions	≤ 2	Reference		Reference	
	>2	1.75 (1.09-2.82)	.021[a]	1.61 (0.96-2.71)	.070
Number of ED visits	0	Reference		-	-
	1-5	1.11 (0.74-1.67)	.619	-	-
	>5	1.36 (0.60-3.06)	.462	-	-
Non-eye care missed appointment rate	≤10%	Reference		Reference	
	>10%	1.38 (0.92-2.07)	.125	1.61 (1.03-2.53)	.038[a]
	No data	1.04 (0.44-2.47)	.929	1.72 (0.66-4.48)	.269
First HbA1c	<6.5	Reference		-	-
	6.5-7.9	0.59 (0.25-1.41)	.237	-	-
	8-9.9	0.78 (0.34-1.80)	.564	-	-

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TABLE 2. Univariate and Multivariate Logistic Regression Models for Predictors of LTFU in Patients Treated for PDR (*Continued*)

Variable	Categories	Univariate Model		Multivariate Model	
		Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
	≥10	0.73 (0.32-1.68)	.462	-	-
	Unreported	0.61 (0.24-1.58)	.311	-	-
Diabetes type	Type 1	Reference		-	-
	Type 2	0.91 (0.42-1.96)	.807	-	-
History of vitreous hemorrhage	No	Reference		-	-
	Yes	0.88 (0.56-1.38)	.570	-	-
History of NVI/NVG	No	Reference		-	-
	Yes	0.61 (0.38-0.95)	.030[a]	-	-
Treatment modality	IVI	Reference		Reference	
	PRP	1.65 (0.96-2.83)	.068	1.93 (1.06-3.50)	.031[a]
	Both	1.14 (0.72 -1.80)	.573	1.27 (0.77-2.11)	.355
Longest recommended follow-up time	≤6 Months	Reference		-	-
	>6 Months	0.66 (0.24 – 1.80)	.417	-	-
Best Initial visual acuity	≥20/40	Reference		Reference	
	20/50-20/200	0.66 (0.42-1.02)	.061	0.68 (0.42 -1.11)	.123
	<20/200	0.55 (0.19-1.61)	.277	0.33 (0.09-1.18)	.088
Best final visual acuity	≥20/40	Reference			
	20/50-20/200	0.54 (0.35-0.84)	.006[a]		
	<20/200	0.95 (.42-2.14)	.901		
Change in visual acuity	Worsened	Reference			
	Improved	0.77 (0.41-1.45)	.415		
	No change	0.81 (0.49-1.31)	.383		

ED = emergency department; HbA1c = hemoglobin A1c; IVI = intravitreal injection; LTFU = lost to follow-up; NVG = neovascular glaucoma; NVI = neovascularization of the iris; PCP = primary care physician; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation.

[a]Statistically significant, $P < .05$.

alone and 183 patients (43.78%) who received both IVIs and PRPs. Patients who received IVIs alone had a mean of 5.8 (±7.6) injections, whereas patients who received PRP alone had a mean of 1.8 (±1.2) sessions of laser treatment. Patients who received both procedures had a mean of 2.4 (±1.5) PRP sessions and 4.5 (±4.0) IVIs. Median total follow-up time was 2.79 (interquartile range [IQR], 1.59, 3.64) years for patients who received IVIs alone, 2.50 (IQR, 1.30, 3.41) years for patients who received PRP alone, and 2.69 (IQR, 1.73, 3.54) years for patients who received both IVIs and PRP. For patients who were LTFU, the mean time of LTFU for those who received IVIs alone, PRP alone, and both IVIs and PRP was 346 days (±190 days), 379 days (±219 days), and 319 days (±145 days), respectively.

• **PATIENT CHARACTERISTICS AND ASSOCIATIONS WITH LTFU BY UNIVARIATE ANALYSIS:** Variable associations with LTFU by univariate analysis are summarized in Table 2.

• **DEMOGRAPHIC FACTORS:** There were no significant differences in LTFU by sex or race. Non-English speaking patients had significantly higher rates of LTFU (66%) than English speaking patients (57%) ($P = .045$). Patients 55 years old or younger had the lowest rate of LTFU at 54%, compared to 67% for patients 56-65 years old ($P = .014$) and 68% for patients older than 65 ($P = .024$).

• **SOCIAL FACTORS:** There were no statistically significant differences in LTFU based on history of psychiatric illness, substance abuse disorder, homelessness, or food pantry visits. Patients with a documented history of noncompliance had significantly higher rates of being LTFU (68%) than those without (56%) ($P = .012$).

• **ECONOMIC FACTORS:** Although there was variability in LTFU based on patient insurance, rates of LTFU were only significantly different between patients with unreported insurance (51%) and commercial insurance (68%) ($P = .032$). Patients whose home ZIP code was 20 miles or less from the authors' institution had a significantly higher rate of being LTFU (64%) than those living farther than 20 miles away (39%) ($P = .003$). Analysis did not find a significant relationship between LTFU and average household income.

• **HOSPITAL FACTORS:** LTFU rates were significantly higher in patients with a PCP located at the authors' institution (63%) compared to those with a PCP outside the authors' institution (51%) ($P = .047$). Patients with greater than 5 comorbidities on their problem list had significantly higher LTFU rates (80%) than those with 5 or fewer comorbidities (59%) ($P = .004$). Patients who were seen by 20 or more distinct departments at the authors' institution had significantly higher rates of LTFU (88% vs. 59%, respectively; $P = .004$). Patients with more than 2 inpatient or observation unit admissions during the study period had significantly higher LTFU rates (71%) than those with 2 admissions or fewer (58%) ($P = .021$). The study did not find a significant relationship between LTFU and PCP status, number of ED visits, or rate of non-eye care missed appointments.

• **CLINICAL FACTORS:** There were no statistically significant differences among rates of LTFU based on HbA1c level, diabetes type, history of vitreous hemorrhage, treatment modality received, or recommended follow-up time. Patients with no history of NVI or NVG had significantly higher rates of LTFU ($P = .030$).

• **VISION OUTCOMES:** There were no significant differences in rates of LTFU based on BIVA. Similarly, there were no significant differences in LTFU rates between patients whose VA worsened, improved, or remained stable during the study period. Patients with good BFVA (20/40 or better) were significantly more likely to be LTFU than patients with intermediate BFVA (20/50-20/200; 65% vs. 50%; $P = .006$).

• **MULTIVARIATE MODEL FOR PREDICTING LTFU:** A summary of the multivariate model for predicting LTFU is included in Table 2. All variables with global significance or individual category significance of $P < .2$ were included in the multivariate model. These variables were: race, primary language, age, history of noncompliance, insurance type, distance from institution, PCP on file, PCP at the same institution, number of comorbidities, number of departments seen, number of inpatient/observation admissions, non-eye care missed appointment rate, history of NVI or NVG, treatment modality received, and BIVA. We chose to not include the variable BFVA in the multivariate analysis as it is a patient characteristic that would be unavailable to clinicians when making treatment decisions early in the course of a patient's care.

Based on the multivariate analysis, statistically significant variables associated with higher LTFU rates included non-English primary language (odds ratio [OR], 1.83; 95% confidence interval [CI], 1.19-2.82; $P = .006$), age 56-65 (vs. age ≤55) (OR, 1.86; 95% CI, 1.13-3.05; $P = .014$) and age older than 65 years (vs age ≤55) (OR, 1.94; 95% CI, 1.08-3.48; $P = .027$), shorter distance lived from institution (OR, 2.68; 95% CI, 1.27-5.63; $P = .009$), number of comorbidities greater than 5 (OR, 2.38; 95% CI, 1.07-5.29; $P = .034$), number of departments seen of 20 or greater (OR, 4.66; 95% CI, 1.52-14.28; $P = .007$), and non-eye care missed appointment rate greater than 10% (OR, 1.61; 95% CI, 1.03-2.53; $P = .038$). Additionally, patients who received only PRP during the study period were almost twice as likely to be LTFU compared to patients who received only IVIs (OR, 1.93; 95% CI, 1.06-3.50; $P = .031$). There were no statistically significant differences in LTFU rates between patients who received both procedures and those who received only IVIs or PRP.

DISCUSSION

TO DATE, THIS IS THE MOST COMPREHENSIVE STUDY EXAMining risk factors for LTFU in patients being treated for PDR. Many of the variables assessed in this study have not been examined in this context previously in the medical literature. Specifically, variables unique to the present study include: primary language, history of mental illness and substance use; homelessness and food insecurity; insurance type; history of noncompliance and missed appointments in other clinics; history of NVI/NVG and vitreous hemorrhage; number of comorbidities; number of departments seen; PCP status; and number of ED visits and hospital admissions. Many of these factors may be more prevalent in the authors' urban population than in the general population.

This study found that 61% of the included patients with PDR requiring treatment with IVI and/or PRP had at least 1 episode of LTFU exceeding 6 months over approximately a 4-year time span, with 25% lost for over 12 months. In comparison, a recent study by Angermann and associates[8] found that 28.8% of patients receiving IVIs for PDR were LTFU for more than 6 months, and 18.9% were lost for more than 12 months. Similarly, another study by Obeid and associates[7] found that 25.4% of patients with PDR were lost for greater than 12 months immediately after receiving either PRP or an IVI. Compared to other studies, we chose to examine a LTFU time frame of greater than 6 months because the authors believed a 12-month cutoff would exclude too many patients with potentially harmful gaps in their treatment regimens. LTFU incidence was also examined at any point in the study period, as opposed to immediately post-procedure, to better capture this important data.

The rates of patients who were LTFU in the present study and in others are substantially higher than those seen in clinical trials, which range from 5%-10%.[1,2] There are multiple possible explanations for this disparity including selection bias, with study patients being potentially more motivated to comply with treatment.[7] Because the treatment of PDR requires frequent therapeutic intervention, understanding the extent of LTFU in these patients is important in optimizing visual outcomes. Additionally,

TABLE 3. Distribution of Insurance Type by Age

		Insurance Type				
Age, y	Commercial	Medicare	Medicaid	Free Care	Unreported	Total
≤55	21 (11%)	27 (15%)	96 (52%)	6 (3%)	35 (19%)	185
56-65	19 (14%)	37 (26%)	50 (36%)	5 (4%)	29 (21%)	140
>65	23 (25%)	29 (31%)	19 (20%)	1 (1%)	21 (23%)	93

identifying patients at high risk for LTFU is potentially important to consider when selecting treatment regimens.

The authors' data confirms studies from other medical specialties that have identified non-English language as a predictor of LTFU.[16,17] This result does not necessarily come as a surprise, as non-English speakers may have more difficulties understanding follow-up instructions, despite the use of interpreter services, and are more likely to have social barriers to care[18] and decreased health care use.[19,20]

In the present patient population, age younger than 55 years old predicted a lower rate of LTFU when compared to older patients. Conversely, many other studies have found that LTFU rates decrease with increasing age[7,12,21] and suggest that increased adherence in those older than 65 is likely due, at least in part, to higher rates of insurance coverage as a result of Medicare. Due to universal state healthcare, Massachusetts has the lowest rate of uninsured adults younger than 65 in the country.[22] In the present study population, 77.8% of patients younger than 55 had a documented form of insurance compared to 76.4% of patients older than 65 (Table 3). Interestingly, the finding of increased visit adherence in the younger age group aligns with that found in one recent study of patients being treated for PDR in a universal health care environment outside of the United States. With insurance status removed as a potential barrier, the authors suggest that lower visit adherence among older patients may be a reflection of the increased comorbidities, lack of mobility, or assistance requirements associated with increasing age.[8]

Several studies have indicated that comorbid illnesses contribute to patient nonadherence with intravitreal injection schedules for diabetic macular edema and age-related macular degeneration.[23,24] Patients with multiple comorbidities may face physical, emotional, or financial barriers to self-care resulting in challenges to adherence.[25,26] Sicker patients likely have more physician visits and hospitalizations, both of which may lead to missed eye care appointments.

Surprisingly, longer travel distance to the clinic was associated with lower rates of LTFU in the present cohort. Although seemingly counterintuitive, this trend has been seen in at least one other study investigating missed appointments in an urban hospital.[27] The present authors hypothesize that the demographics of the area surrounding the authors' city hospital may help to explain this association. Patients living in close proximity to the authors' inner city hospital may represent a more impoverished population with increased social barriers to care. Although the study did not find that AHI by zip code was a significant predictor in the present model, it is possible, that high income disparity within the zip codes surrounding the authors' hospital make AHI an imperfect measurement of actual patient income.

No significant associations were found between initial visual acuity and LTFU. This result is in contrast to those found in the study by Obeid and associates[7] in which improved adherence was associated with worse presenting acuity in the treated eye. However, when BIVA was measured, the present study used the better seeing eye (not necessarily the PDR-treated eye), which may have affected this study's results, as patients with good binocular vision may not feel urgency for follow-up. In the present study, patients with an intermediate level of BFVA (measured in the better seeing eye with PDR) were less likely to be LTFU than those with good acuity. Again, one could conjecture that asymptomatic patients with good VA may be less likely to show up for their appointments. Finally, these results demonstrated no significant association between LTFU and change in VA over the study period. However, significant variations in total follow-up time between patients along with failure to control for disease severity may cloud interpretation of these data.

Interestingly, analysis revealed that patients who received only PRP were more likely to be LTFU than those who received only IVIs, a finding also reported by Obeid and associates.[7] This association may reflect a selection bias as clinicians may have chosen to forgo IVI in patients whom they felt were less likely to follow-up consistently. Second, it has been suggested that the pain[28] and lower levels of patient satisfaction[2] associated with PRP may discourage patients from appropriate follow-up.[8] Third, because PRP has a more lasting treatment effect, it is possible that these patients go longer before developing symptoms that prompt them to return to care.

Finally, the present study found a positive association between the frequency of missed appointments outside of the eye clinic with LTFU in the authors' vitreoretinal clinic. While history of missed appointments within the same clinic has been shown to predict future no-shows,[29,30] to the authors' knowledge, there have been few studies to evaluate the predictive value of attendance history in outside clinics. This could be a useful measurement when trying to predict adherence of a new patient with no history of care in the eye clinic.

Our present study has limitations. The patient data collected about the present cohort is limited by what can be obtained from the electronic medical record. Variables such as comorbidities, psychiatric history, substance abuse history, and homelessness depend on the accuracy of a patient's EMR problem list, which may not be completely comprehensive. Variables such as number of departments seen, number of admissions, missed appointment rate in

other clinics, ED visits, history of noncompliance, and food pantry visits do not account for care received outside of the authors' institution and, thus, may underestimate the data for some patients. Additionally, it is possible that some patients may receive ophthalmic care outside the authors' institution during periods of presumed LTFU. Finally, the present study is retrospective and not randomized with significant variations in duration of patient follow-up which may impact results.

The results of this study identify several risk factors for patients with PDR who are LTFU that have not been previously studied. These risk factors highlight particularly vulnerable groups of patients who may be more susceptible to being LTFU and poorer visual outcomes. Identifying patients at high risk for LTFU may be an important consideration for choosing treatment modality and patient counseling. Although it is vital to emphasize to patients that neither PRP nor IVI is a "one-and-done" treatment for PDR, more studies directed at comparing the clinical outcomes of patients who are LTFU may help determine how we can best mitigate the harmful consequences of gaps in treatment.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

MICHAEL GREEN: INVESTIGATION, FORMAL ANALYSIS, Writing - original draft. **Thomas Tien:** Investigation, Writing - review & editing. **Steven Ness:** Conceptualization, Methodology, Writing - review & editing, Supervision.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported.

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