Diabetic Retinopathy as a Potential Risk Factor for Ptosis: A 13-Year Nationwide Population-Based Cohort Study in Taiwan

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Abstract

Background: To investigate whether patients with diabetic retinopathy (DR) or other possible clinical factors are at increased risk of ptosis.

Methods: Data was collected from the Taiwan National Health Insurance system and included patients newly diagnosed with DR between 2000 and 2012. The endpoint of interest was a diagnosis of ptosis.

Results: Follow-up data of 9,494 patients with DR and 37,976 matched comparisons (non-DR) from 2000 to 2012 were analyzed. Patients with DR were found to have a significantly higher cumulative incidence of ptosis (Kaplan-Meier analysis, log-rank test $p < 0.001$). With Cox regression analysis, the DR group was found to have higher risk of developing ptosis (adjusted hazard ratio (HR) [95% CI]: 2.76 [1.74-4.38], $p < 0.001$) when compared to the control cohort. Higher risks of developing ptosis in patients with DR were found in female patients and in adult patients of all age groups. When stratified by comorbidities, the influence of DR was more prominent for non-smokers. Patients with DR had a higher risk of developing ptosis compared to matched controls, regardless of whether they had lipid metabolism disorders and hypertension.

Conclusions: Patients with DR were found to have higher risk of developing ptosis in this cohort study. Thus, patients with DR should be vigilant for symptoms of ptosis. For female patients, adult patients, or patients without smoking, the association of DR with ptosis development is even stronger. Before ptosis surgery, the possibility of underlying diabetes or DR should be also scrutinized and treated properly to avoid undesirable postoperative dissension.

Précis

DR may increase the risk of subsequent ptosis. Although gender or age also are possible risk factors associated with ptosis, DR plays a pivotal role in ptosis development, especially for female, adults, and non-smokers.

Background

Diabetes mellitus (DM) is a global health problem. At present, there are about 425 million diabetic patients in the world, and this number is projected to reach 629 million by the year 2045.[1] The prevalence of DM in the Taiwanese population over the age of 18 is 11.8%. Diabetic retinopathy (DR), a microvascular complication of DM that develops over time, is the leading cause of blindness in people aged 20 to 64.[2]

Common symptoms of DR include blurry vision and floaters. Although DR usually affects both eyes, it often goes undetected in the early stages. By the time symptoms appear, DR can already be at an advanced stage and may have caused irreversible damage.[3, 4, 5] Taiwan's Bureau of National Health

Insurance (NHI) has designed DR screening programs with appropriate and timely referral to facilities with trained eye care professionals to achieve early diagnosis in the majority of diabetic patients.

Ptosis is a drooping of the upper eyelid. The most common cause of ptosis in adults is the separation or stretching of the levator muscle tendon from the eyelid. Ptosis may be due to myogenic, neurogenic, aponeurotic, mechanical or traumatic causes. Adult ptosis may occur as a complication of other diseases involving the levator muscle or its nerve supply, such as neurological and muscular diseases.[6]

Ptosis related with DM had been reported in 1965.[7] Since then, several short-term reports have addressed the relationship between DM and ptosis.[8-16] In the literature, few published report has addressed the relationship between DR and ptosis. Therefore, we conducted a 13-year nationwide cohort study by analyzing claims data from the Taiwan National Health Insurance Research Database (NHIRD) with ICD-9 codes to investigate whether there is an association between DR and ptosis in the Taiwanese population.

Methods

Data source

The Longitudinal Health Insurance Database (LHID), established by the National Health Research Institute (NHRI) in Taiwan, contains patient records of over 99% of the Taiwanese population. The data, derived from across all medical care settings, include information on demographics, diagnoses, and medical procedures and prescriptions. We obtained these records through a formal application to the Health and Welfare Data Science Center (HWDC), Department of Statistics, Ministry of Health and Welfare, Taiwan (http://dep.mohw.gov.tw/DOS/np-2497-113.html). We did not have any special access privileges that others would not have, and interested researchers would be able to access the data in the same manner.

To comply with the Personal Information Protection Act, identifying information of each insurant in the LHID was re-coded. Data files were linked with the identifications of patients that were scrambled with surrogate numbers to protect the confidentiality of the beneficiaries. Therefore, informed consent was subsequently waived. The study protocol was conducted according to the principles described in the Declaration of Helsinki. This study has been approved by the Research Ethics Committee at China Medical University Hospital, Taiwan (CMUH104-REC2-115-AR-4).

Study subjects

To perform this cohort study, we selected patients newly diagnosed with DR [the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) 362.0, 362.01 and 362.02] between January 1, 2000 and December 31, 2012. Patients with at least three outpatient visits for DR were defined as new cases and the first visit date for DR was defined as the index date. Those with a diagnosis of DR prior to 2000 were excluded. The endpoint was a new diagnosis of ptosis (ICD-9-CM 374.3, 374.30, 374.31, and 374.32). The end date of follow-up was December 31, 2013.

Those with a history of ptosis (ICD-9-CM 374.3, 374.30, 374.31, and 374.32) were excluded. Patients with viral hepatitis (ICD-9-CM code 070), cirrhosis (ICD-9-CM code 571, A347), interferon treatment, human immunodeficiency virus (HIV) infection (ICD-9-CM code 042-044, 795.8, V08), tuberculosis (ICD-9-CM code 010-012), syphilis (ICD-9-CM code 091.0, 095.4, 095.8), systemic malignancy (ICD-9-CM code 140-208), autoimmune diseases (ICD-9-CM code 135, 279.49, 283, 443, 571.42, 696, 710, 714, 715), chronic Obstruction Pulmonary Disease (ICD-9-CM code 490-492, 494, 496), and asthma (ICD-9-CM code 493, 494) were also excluded.17 Subjects without outpatient visits for eye diseases were also excluded.

The comorbidities assessed included current smoking (ICD-9-CM code V15.82, 305.1, 794.2), lipid metabolism disorders (ICD-9-CM code 272), and hypertension (HT) (ICD-9-CM code 401-405, A26). Patient identification numbers were encrypted for privacy protection.

Controls were randomly selected from populations without histories of viral hepatitis, interferon treatment, HIV infection, tuberculosis, syphilis, or ptosis. They were frequency-matched by age group (<20, 20-39, 40-64 and 65+ years old), gender, ophthalmologic outpatient department (OPD) before the index date, and index-year at a ratio 4:1. Only patients with at least one ophthalmology clinic visit before enrolling in the study were included. We then matched the ophthalmologic OPD visits between both groups.

Study endpoint

The clinical endpoint was a diagnosis of ptosis. Patients with at least two outpatient visits for ptosis, separated for at least 7 days, were defined as the endpoint to ensure the validity of the diagnosis. All study subjects were followed from the index date until the endpoint. Those without endpoint development were followed until the date of withdrawal from the program or the end of 2012, whichever occurred first. In this study, the demographic characteristics included age group (<20, 20-39, 40-64 and 65+ years old), gender, comorbidities, and ophthalmologic OPD before the index date.

Statistical analyses

We used chi-square testing to determine the difference of demographic characteristics between the DR cohort and comparison cohort from 2000 to 2012. A t-test was employed for the difference of the mean OPD visit for ophthalmology between two cohorts. Continuous variables, such as age and follow-up time, were shown as mean and standard deviation (SD) and analyzed by using the Wilcoxon rank sum test. The cumulative incidences of ptosis for both the DR and comparison cohorts were estimated by using the Kaplan-Meier method. The difference between the two curves was examined by using the log-rank test. A multivariable Cox model was adjusted for continuous age, gender, comorbidities, and OPD visits for ophthalmology before the index date. Univariate and multivariable cox proportional regression analysis were used to measure the hazard ratio (HR) and 95 % confidence interval (CI) to assess the association between DR and the risk of developing ptosis. The incidence density rate of ptosis (per-1,000 years) was calculated for DR cohort and comparison cohort. The risk of ptosis in the DR and comparison cohorts was stratified by age group, gender, and comorbidities, using Cox proportional hazard regression. SAS

software (version 9.4 for Windows; SAS Institute, Cary, NC, USA) was used for all statistical analyses and creation of Kaplan-Meier survival curves. A two-sided $P < 0.05$ was considered statistically significant. The Wilcoxon rank-sum test was used for verification of average age and follow-up time.

Results

Baseline data

Follow-up data of 9,494 patients with DR and 37,976 matched comparisons (non-DR) from 2000 to 2012 were analyzed. The gender and age distributions were comparable in both groups according to initial grouping design (Table 1). The follow-up time (year) was 6.93 ± 3.81 (mean ± SD) in DR group and 7.02 ± 3.83 in non-DR group ($p=0.04$) (Table 1). As for comorbidities, the proportion of patients with lipid metabolism disorders or patients with hypertension were higher in the DR group than in the non-DR group (DR vs. non-DR: 17.9% vs. 6.52%, $p < 0.01$ for lipid metabolism disorders and 24.8% vs. 12.8%, $p < 0.01$ for hypertension, Table 1).

Time to event analysis

Using Kaplan-Meier survival statistics, crude overall survival curves showed that cumulative incidence of ptosis was significantly higher in the DR group (log-rank test $p < 0.001$, Figure 1). After adjusting for confounding factors, patients with DR were still found to have significantly a higher cumulative incidence of ptosis (Kaplan-Meier analysis, log-rank test $p < 0.001$, Figure 2). With Cox regression analysis, the DR group was found to have higher risk of developing ptosis (adjusted hazard ratio (HR) [95% CI]: 2.76 [1.74-4.38], $p < 0.001$) when compared to the control cohort (Table 2).

The role of DR after stratification

When comparisons of the DR and non-DR groups were stratified by gender and age, higher risks of developing ptosis patients with DR were found in female patients (adjusted HR 3.38 [1.89-6.04], $p < 0.001$, Table 3) and in adult patients of all age groups (adjusted HR: age 20-39, 3.07 [1.06-8.86], $p<0.05$; age 40-64, 2.34 [1.08-5.06], $p<0.05$; age≥65, 2.53 [1.24-5.18], $p<0.05$, Table 3). When stratified by comorbidities, the association of DR was stronger in non-smokers (adjusted HR 2.76 [1.74-4.38], Table 3); but for lipid metabolism disorders and hypertension, patients with DR had higher risk of developing ptosis compared to matched controls, regardless whether they had either of these two major comorbidities (Table 3).

Other possible clinical factors related to ptosis

In addition to DR, we also found some clinical factors that might have impacts on the occurrence of ptosis in the Cox regression analysis (Table 2). For example, males were found to have higher risk of ptosis than females (adjusted HR for male: 1.67 [1.06-2.63], $p < 0.05$), and older subjects (age ≥ 40) were found to have higher risk of ptosis than their younger counterparts (adjusted HR for age 40-64: 4.71 [1.11-19.9], $p < 0.05$, adjusted HR for age ≥ 65: 20.7 (4.80-89.4), $p < 0.001$). After adjusting for confounding

factors, we did not find smoking, lipid metabolism disorders, and hypertension to contribute additional risk to ptosis development (Table 2).

Discussion

DM is a common condition with potentially devastating health consequences that affect all populations worldwide.[1, 2] It may result in diverse ophthalmological problems including ptosis, DR, and more severe findings involve cranial neuropathies.[13] The primary intraocular manifestations of DM are DR and cataracts.[3-5] According to the National Eye Institute, DR is the most common diabetic eye disease and the leading cause of blindness in American adults.

Earlier, DR was believed to be caused by changes in the blood vessels of the retina. Recently, DR has been understood as neurovascular degeneration or sensory neuropathy akin to other peripheral sensory neuropathies,[3] with impairment of the retinal neurons as the final cause of vision impairment. Nonetheless, the primary clinical manifestations of DR are the vascular features of microaneurysms, hemorrhages, cotton wool spots, and eventual retinal neovascularization.

Bosco and colleagues have reported that prediabetic status may be a risk factor for developing ptosis.[12] The Korea National Health and Nutrition Examination Survey (KNHANES), conducted in 2009 and 2010, has found that DM is an independent risk factor for ptosis in the general Korean population.[14] Another study of KNHANES also revealed DM had statistically significant association with ptosis adjusting all other confounders.[15]

Diabetic neuropathy is one of the most common long-term complications of DM. The prevalence of diabetic neuropathy varies with both the severity and duration of hyperglycemia.[18] Approximately 50% of diabetic patients will eventually develop neuropathy.[19] The most common diabetic cranial mononeuropathy occurs especially in oculomotor nerve and the superior division innervates the superior rectus and levator palpebrae superioris.[20]

The etiology of diabetic neuropathy is hyperglycemia-induced damage to nerve cells and neuronal ischemic change.[20] DM also affects the motor component of the visual system via cranial nerve palsies. Diabetic oculomotor nerve palsy is one of the most common etiologic subset of oculomotor nerve palsy in adults.[16] Oculomotor nerve palsy associated with DM typically cause ptosis and diplopia. Ptosis may be the only manifestation of the superior division oculomotor nerve palsies.[16]

In diabetic oculomotor nerve palsy, infarctions initially occur in the smallest vessels that supply the interior portion of the oculomotor nerve. It seems that ischemic lesions of the precavernous nerve could selectively affect nerve fibers innervating only the levator palpebrae superioris,[21] implying that the most interior portion of the oculomotor nerve may consist of nerve fibers innervating the levator palpebrae superioris.[16]

The other pathogenesis of ptosis in DM might be chronic tissue hypoxia causing levator palpebrae muscle damage, in which thickening of the capillary basal membranes may be one of the factors.[9] DR usually develops in parallel with neuropathic complications. After adjusting for confounding factors, our study demonstrated DR to be associated with significantly higher cumulative incidence of ptosis. Smoking, lipid metabolism disorders, or hypertension did not appear to contribute any risk to the development of ptosis.

When stratified by comorbidities, the influence of DR was more prominent for non-smokers, regardless of the presence of lipid metabolism disorders or hypertension. The hazards of cigarette use arise from the abundance of free radicals, polycyclic aromatic hydrocarbons, and other reactive compounds that activate pro-inflammatory pathways and trigger pathological processes.[22, 23] Oxygen free radicals can induce vascular inflammation and have been implicated in a number of systemic disease processes. Smoking associated with the development of cranial autonomic symptoms including ptosis had been reported which might minimize the effects of DR.[24]

Our study has a few limitations. First, diagnoses of DR and ptosis are based solely on ICD codes. However, Taiwan's Bureau of NHI routinely interviews patients and reviews medical charts to verify diagnoses and quality of care. Since LHIRD claims data are deidentified, we did not contact patients directly for additional information.

Second, the comorbidities between non-DR ischemic retinopathy and DR cannot be definitively excluded. However, diagnostic bias could be reduced due to codes specific for DR, ptosis, and other ischemic retinopathy in Taiwan NHIRD. Laboratory data were not used in our analyses due to their unavailability through LHIRD.

Third, information on the duration and quantity of exposure to cigarette smoke was not available in the LHIRD. This precluded detection of a dose-dependent association between smoking, DR, and ptosis.

Fourth, these findings may only pertain to the Taiwanese population and thus similar studies should be performed in different countries to see if the association holds.

Nevertheless, this also demonstrates the originality of this research. In spite of these limitations, the availability of data on a number of potential risk factors and the large sample size are important strengths of our study that add plausibility to the findings.

In conclusion, our 13-year cohort study found that patients with DR have higher risk of developing ptosis. Thus patients with DR should be monitored for the symptoms of ptosis. For female patients, adult patients, or patients without smoking, the association of DR with ptosis development might be even stronger. Before ptosis surgery, the possibility of underlying diabetes or DR should be also scrutinized and treated properly to avoid undesirable postoperative dissension.

List Of Abbreviations

DR: diabetic retinopathy, DM: diabetes mellitus, NHI: National Health Insurance, NHIRD: National Health Insurance Research Database, ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification, LHID: Longitudinal Health Insurance Database, HIV: human immunodeficiency virus, OPD: outpatient department, SD: standard deviation, HR: hazard ratio, CI: confidence interval, KNHANES: Korea National Health and Nutrition Examination Survey, HWDC: Welfare Data Science Center.

Declarations

Ethics approval and consent to participate

The need for approval was waived due to deidentification.

Consent for publication

Written informed consent for publication was waived due to deidentification.

Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

CJL, PTT, CHC, CTL, NYH, YCY, HB, HSC, WLC, YYT were responsible for substantial contributions to the conception or design of the work, and acquisition of data. CJL, PTT, CHC, YCY, HSC were responsible for interpretation of results. CJL, CHC, YCY, HB, HSC participated in the design and was a major contributor in writing the manuscript. CJL, PTT, CHC, CTL, NYH, YCY, HB, HSC, WLC, YYT were responsible for final approval of the version to be published. All authors reviewed and approved the final manuscript.

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Declaration of interest statement

The authors have no proprietary or commercial interest in any materials mentioned in this article. The authors were involved in design and conduct of study; data collection; analysis, management, and interpretation of data; and preparation, review, and approval of manuscript.

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Tables

Table 1. Baseline characteristics of patients

	Diabetic retinopathy (n=9,494)		Non-diabetic retinopathy (n=37,976)		p-value*
	n	%	n	%	
Gender					>0.99
Male	4719	49.7	4719	49.7	
Female	4775	50.3	4775	50.3	
Age, years					>0.99
<20	979	10.3	3916	10.3	
20-39	3372	35.5	13488	35.5	
40-64	4092	43.1	16368	43.1	
≥65	1051	11.1	4204	11.1	
mean(SD)†	42.5 (17.5)		42.4 (17.5)		0.46
Comorbidity					
Current smoke	40	0.42	145	0.38	0.58
Lipid metabolism disorders	1704	17.9	2476	6.52	<.01
Hypertension	2362	24.8	4859	12.8	<.01
Follow-up time, year†	6.93 (3.81)		7.02 (3.83)		0.04

Diabetes mellitus included type 1 and type 2 diabetes mellitus.

*P-value using *chi-square* for the comparisons between with and without diabetic retinopathy.

†Average age and follow-up time using *Wilcoxon rank-sum test* for verification.

Table 2. Cox model measured hazard ratios and 95% confidence interval of ptosis associated with gender and age.

Variable	Ptosis			Crude HR (95%CI)	Adjusted HR (95%CI)
	Event	PY	IR		
Diabetic retinopathy					
No	47	266927	0.17	**1(reference)**	**1(reference)**
Yes	33	65860	0.50	2.84 (1.82-4.43)***	2.76 (1.74-4.38)***
Gender					
Female	31	161415	0.19	**1(reference)**	**1(reference)**
Male	49	171372	0.28	1.49 (0.95-2.34)	1.67 (1.06-2.63)*
Age, years					
<20	2	42460	0.04	**1(reference)**	**1(reference)**
20-39	14	130050	0.10	2.28 (0.52-10.0)	2.19 (0.49-9.66)
40-64	30	130611	0.22	4.91 (1.17-20.5)*	4.71 (1.11-19.9)*
≥65	34	29666	1.14	24.6 (5.90-102.7)***	20.7 (4.80-89.4)***
Comorbidity					
Current smoke					
No	0	739	0	**1(reference)**	**1(reference)**
Yes	80	332048	0.24	--	--
Lipid metabolism disorders					
No	68	311260	0.21	**1(reference)**	**1(reference)**
Yes	12	21527	0.55	2.53 (1.36-4.70)**	0.84 (0.43-1.63)
Hypertension					
No	50	292057	0.17	**1(reference)**	**1(reference)**
Yes	30	40730	0.73	4.30 (2.73-6.78)***	1.43 (0.83-2.44)

PY, person-years; IR, incidence rate, per 1,000 person-years; HR, hazard ratio; CI, confidence interval;

HR adjusted for gender, age and comorbidities.

*p<0.05, **p<0.01, ***p<0.001

Table 3. Incidence rate and hazard ratio of ptosis between with and without diabetic retinopathy stratified by gender, age and comorbidities.

Variable	Diabetic retinopathy						Crude HR (95%CI)	Adjusted HR (95%CI)
	No			Yes				
	Ptosis	PY	IR	Ptosis	PY	IR		
Gender								
Male	20	129694	0.15	11	31720	0.34	3.87 (2.14-6.99)***	1.98 (0.92-4.27)
Female	27	137233	0.19	22	34140	0.64	3.27 (1.86-5.74)***	3.38 (1.89-6.04)***
Age, years								
<20	0	33991	0	2	8469	0.23	–	–
20-39	8	103732	0.07	6	26317	0.22	2.96 (1.02-8.55)*	3.07 (1.06-8.86)*
40-64	18	105269	0.17	12	25343	0.47	2.79 (1.34-5.81)**	2.34 (1.08-5.06)*
≥65	21	23935	0.87	13	5731	2.26	2.57 (1.29-5.14)**	2.53 (1.24-5.18)*
Comorbidity								
Current smoke								
No	47	266356	0.17	33	65691	0.50	2.84 (1.82-4.43)***	2.76 (1.74-4.38)***
Yes	0	571	0	0	169	0	–	–
Lipid metabolism disorders								
No	46	254586	0.18	22	56674	0.38	2.14 (1.29-3.56)**	2.24 (1.34-3.76)**
Yes	1	12341	0.08	11	9186	1.19	15.0 (1.94-116.8)**	16.3 (2.10-127.4)**
Hypertension								
No	31	239601	0.12	19	52457	0.36	2.79 (1.58-4.95)***	3.21 (1.79-5.73)***

Yes	16	27326	0.58	14	13403	1.04	1.79 (0.87-3.67)	2.18 (1.05-4.53)*

PY, person-years; IR, incidence rate, per 1,000 person-years; HR, hazard ratio; CI, confidence interval;

HR adjusted for gender, age and comorbidities.

*p<0.05, **p<0.01, ***p<0.001

– Unable to calculate because of there are few or no events in with and without diabetic retinopathy cohort.

Figures

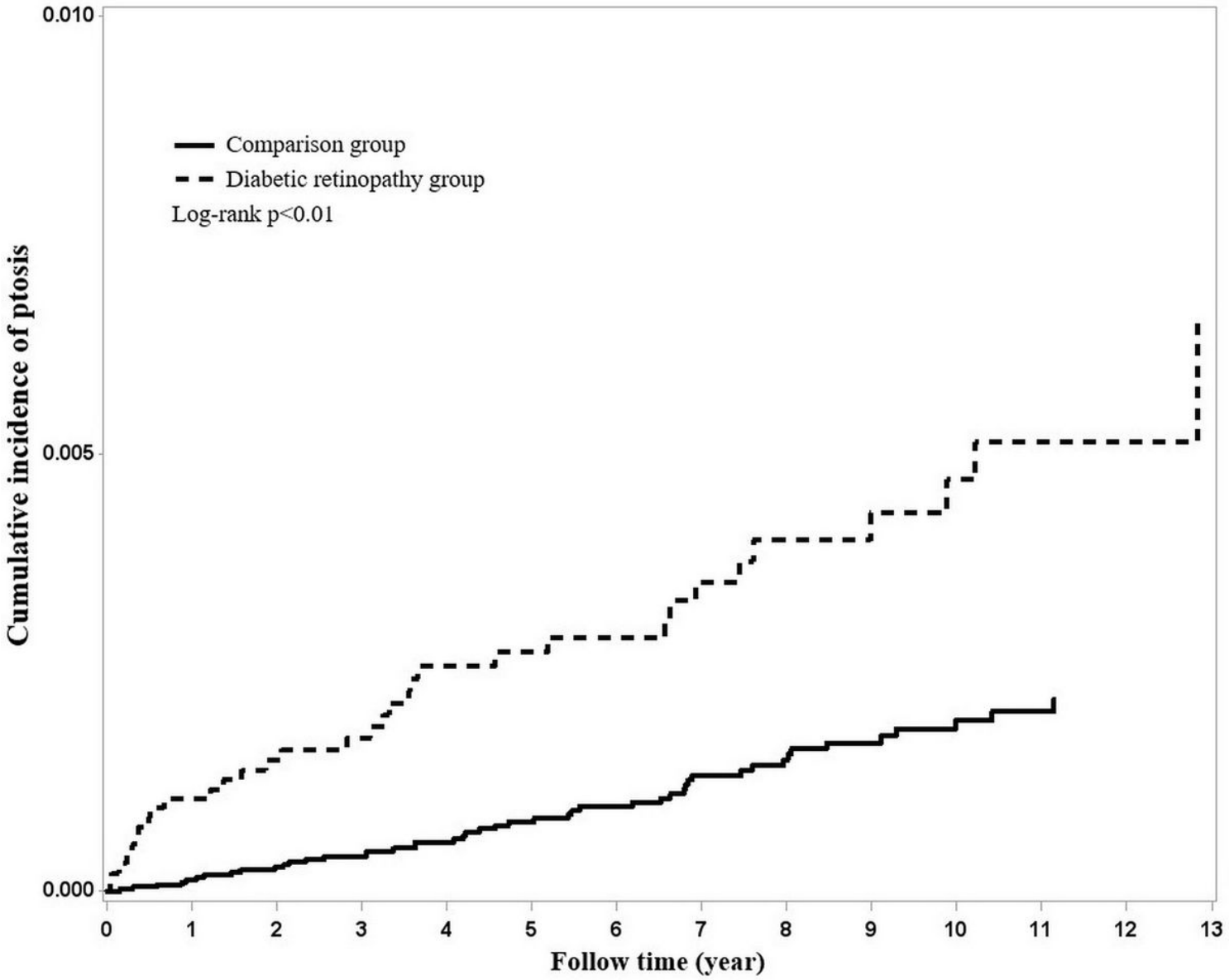

Figure 1

Using Kaplan-Meier survival statistics, it showed crude overall survival curves by with and without diabetic retinopathy. (log-rank P<0.001)

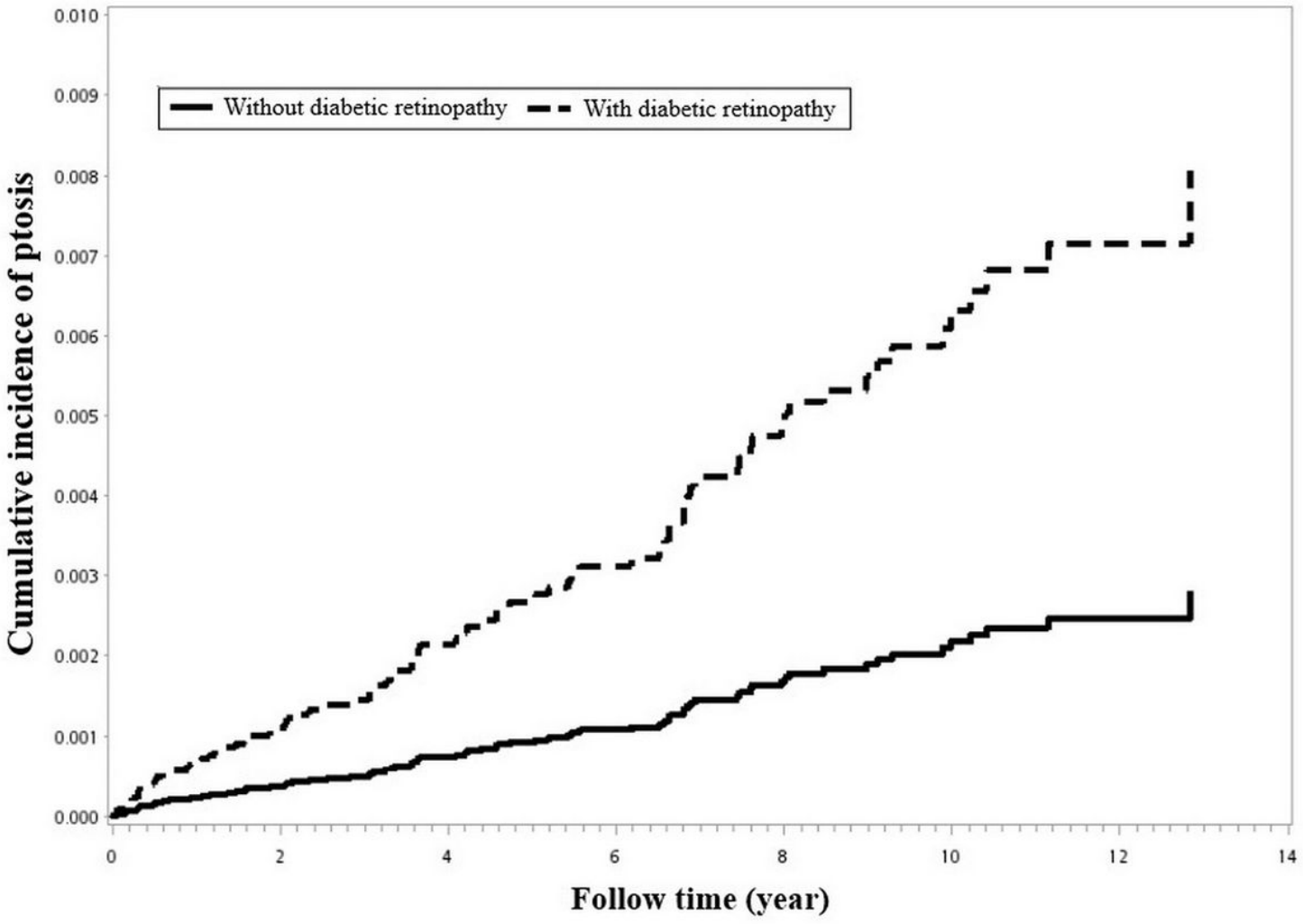

Figure 2

Using Kaplan-Meier survival statistics, it showed adjusted confounding factors survival curves by with and without diabetic retinopathy. (log-rank P<0.001)