Seasonal Variations in the Occurrence of Retinal Vein Occlusion: A Five-Year Nationwide Population-Based Study from Taiwan

JAU-DER HO, CHING-YAO TSAI, SHIOW-WEN LIOU, RAY JUI-FANG TSAI, AND HERNG-CHING LIN

• PURPOSE: **To determine whether seasonal variation exists in the incidence of retinal vein occlusion.**
• DESIGN: **Retrospective, nationwide population-based administrative database study.**
• METHODS: **We collected data on outpatient and emergency visits for the period from January 1999 through December 2003 from the Taiwan National Health Insurance Research Database, a source that covers more than 96% of Taiwan's 23 million citizens. In total, 20,792 patients with a first-time diagnosis of either central retinal vein occlusion or branch retinal vein occlusion (The International Classification of Disease, Ninth Revision, Clinical Modification [ICD-9-CM] code 362.35 or 362.36, respectively) were identified. Monthly incidence of retinal vein occlusion was obtained for each age group, each gender group, and for the entire sample. The autoregressive integrated moving average method of analysis was adopted to examine seasonality in the monthly incidence of retinal vein occlusion.**
• RESULTS: **The monthly incidence rates of retinal vein occlusion revealed significant seasonality, with a clear peak in January for each age group and each gender group, as well as for the total sample.**
• CONCLUSIONS: **Our study demonstrates significant seasonal variations in the retinal vein occlusion incidence, with the peak occurrence in the winter month of January. (Am J Ophthalmol 2008;145:722–728. © 2008 by Elsevier Inc. All rights reserved.)**

RETINAL VEIN OCCLUSIVE DISORDERS, WHICH INclude central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO), collectively constitute one of the major causes of severe vision impairment and blindness.[1–4] The systemic and ocular risk factors associated with retinal vein occlusion have been well studied[5–14]; however, little is known about the triggering factors that may precipitate a retinal vein occlusion event. It has been suggested in a number of the prior studies that an association does exist between low ambient temperature and the occurrence of vascular occlusive diseases in other organs, including stroke[15,16] and acute myocardial infarction.[17,18] All of these diseases previously have demonstrated seasonal variations related to temperature.

To the best of our knowledge, there have been three published hospital-based studies that have investigated seasonal variations in the onset of retinal vein occlusion; however, conflicting conclusions were reached. From a retrospective study of 105 CRVO cases collected over a five-year period from a hospital in London, Lavin and Dhillon found a significantly higher rate of incidence during the six-month period from September through February than for the six-month period from March through August.[19] Based on a prospective study of 1,003 retinal vein occlusion cases collected over an 18-year period from the ocular vascular clinic of the University Hospitals and Clinics in Iowa City, Hayreh and associates found no seasonal variations in the onset of any individual type of retinal vein occlusion or in any combination of types.[20] Finally, from a retrospective study of 460 retinal vein occlusion cases collected over a five-year period from a hospital in Armenia, Malayan and associates concluded that there were no seasonal patterns in the onset of any type of retinal vein occlusion.[21] Using a five-year population-based data set from Taiwan, this study investigated the seasonal variations in the occurrence of retinal vein occlusion.

METHODS

• **STUDY SAMPLE:** This study uses claims data for ambulatory care (outpatient/emergency visits) expenditures, covering the years January 1999 through December 2003, from the Taiwan National Health Insurance Research Database (NHIRD), published by the National Health Research Institute in Taipei. The NHIRD covers all inpatient and outpatient medical benefit claims for more than 96% of the Taiwanese population of 23 million people. A total of 80,391 outpatient or emergency visits for

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From the Department of Ophthalmology, Taipei Medical University Hospital, Taipei, Taiwan (J.-D.H., R.J.-F.T.); the Department of Ophthalmology, Taipei Medical University, Taipei, Taiwan (J.-D.H., S.-W.L., R.J.-F.T.); the Department of Ophthalmology, Taipei City Hospital, Taipei, Taiwan (C.-Y.T., S.-W.L.); the Community Medicine Research Center and Institute of Public Health, National Yang-Ming University, Taipei, Taiwan (C.-Y.T.); the Department of Ophthalmology, National Taiwan University Hospital, Taipei, Taiwan (S.-W.L.); and the School of Health Care Administration, Taipei Medical University, Taipei, Taiwan (H.-C.L.).

Inquiries to Herng-Ching Lin, School of Health Care Administration, Taipei Medical University, 250 Wu-Hsing Street, Taipei, Taiwan; e-mail: henry11111@tmu.edu.tw

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the treatment of retinal vein occlusion were recorded between January 1, 1999, and December 31, 2003, with these visits having been identified from the database by a diagnosis of retinal vein occlusion (The International Classification of Disease, Ninth Revision, Clinical Modification [ICD-9-CM] codes, 362.35 and 362.36). Because the incidence of retinal vein occlusion is quite low among the younger population, data on patients younger than 40 years were excluded from the sample. The study sample also was limited to visits with a first-time diagnosis of CRVO or BRVO (ICD-9-CM codes, 362.35 or 362.36) to exclude revisits for the same disease. Our study sample ultimately comprised 20,792 cases. To study the number of monthly visits for non–retinal vein occlusion but possibly related diseases (including myocardial infarction/ischemic heart disease [ICD-9-CM codes, 410 to 414]; hypertension [ICD-9-CM codes, 401 to 405]; stroke [ICD-9-CM codes, 430 to 438]; and diabetes mellitus [ICD-9-CM code, 250]), all the outpatient/emergency visits for the principal diagnosis of these diseases during the study period were identified from the database. This study used nationwide data from the Population Affairs Administration at the Ministry of the Interior in Taiwan to calculate the rate of incidence of retinal vein occlusion per 100,000 persons.

• **STATISTICAL ANALYSIS:** The monthly retinal vein occlusion rates were calculated for a total of 60 months and were categorized by gender and age groups (40 to 49, 50 to 59, 60 to 69, and 70 years and older). Because seasonality is a general component of time-series patterns, the seasonality of the data was evaluated using the autoregressive integrated moving average method, which describes a univariate time series as a function of its past values and has been used in many earlier studies to test for the presence of seasonality.[22,23]

A general autoregressive integrated moving average model was applied, with order (a, d, b) representing the time series of the retinal vein occlusion incidence rates; orders a and b are the respective autoregressive and moving average operators, whereas order d is the differencing. We began by determining whether the time series is stationary; if it was not stationary, we then transformed it into a stationary time series by applying a suitable degree of differencing (d). The model specifications (a, b) subsequently were determined after examining the autocorrelation function and the partial autocorrelation function of the stationary time series.

After adjusting for the time-trend effect, the autoregressive integrated moving average regression method then was adopted as a means of evaluating the effects of monthly factors on the monthly retinal vein occlusion rates. The monthly factors in the model included dummy variables running from January through December, with a specific month being allocated a value of one and the remaining months being given a value of zero.

TABLE 1. Demographic Characteristics and Outpatient/Emergency Visits for Retinal Vein Occlusion in Taiwan, 1999 through 2003*

Variables	Total No.	%
Year		
1999	2440	11.7
2000	3950	19.0
2001	4392	21.1
2002	4859	23.4
2003	5151	24.8
Gender		
Male	10,983	52.8
Female	9809	47.2
Age group (yrs)		
40 to 49	1893	9.1
50 to 59	4081	19.6
60 to 69	6459	31.1
≥ 70	8359	40.2
Principal diagnosis		
Central retinal vein occlusion (ICD-9-CM code 362.35)	6104	29.4
Venous tributary occlusion (ICD-9-CM code 362.36)	14,688	70.6

ICD-9-CM = The International Classification of Disease, Ninth Revision, Clinical Modification; yrs = years.
*Total sample, 20,792.

The time trend was a count variable numbered from one through 60, according to the time series. Given the parsimony of the models, only statistically significant independent variables were included in the autoregressive integrated moving average regression models. The selection of the final parameters was based on the lowest mean absolute percentage error, or mean absolute error, allowing the choice of the best model from the family of autoregressive integrated moving average regression models. All P values of $< .05$ were considered to be statistically significant.

RESULTS

• **OUTPATIENT OR EMERGENCY VISIT RATES:** As Table 1 shows, during each year throughout the study period, there was a gradual increase in first-time outpatient/emergency visits for retinal vein occlusion, as follows: 2,440 in 1999, 3,950 in 2000, 4,392 in 2001, 4,859 in 2002, and 5,151 in 2003. Males accounted for 52.8% of visits. Patients 70 years of age and older and from 60 to 69 years accounted for 40.2% and 31.1% of retinal vein occlusion cases, respectively. Of the 20,792 patients, 6104 (29.4%) had CRVO (ICD-9-CM code, 362.35) and 14,688 (70.6%) had BRVO (ICD-9-CM code, 362.36).

As Table 2 shows, there was a steady increase in incidence of retinal vein occlusion with increasing age.

TABLE 2. Monthly Mean Values for First-Time Outpatient/Emergency Visits for Retinal Vein Occlusion in Taiwan, 1999 through 2003*

Variables	Monthly Mean	Standard Deviation	Minimum	Maximum
Retinal vein occlusion per 100,000 of the population, by age group (yrs)				
40 to 49	0.89	0.41	0.33	2.54
50 to 59	3.26	1.62	1.53	9.82
60 to 69	7.41	4.03	2.55	24.25
≥ 70	10.52	7.17	4.08	39.91
Retinal vein occlusion per 100,000 of the population, by gender				
Male	4.31	2.61	1.94	14.58
Female	3.91	2.15	1.43	13.44
Total	4.12	2.37	1.78	14.01

Yrs = years.
*Total sample, 20,792.

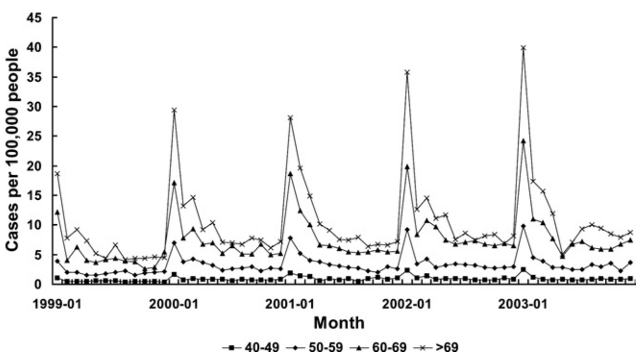

FIGURE 1. Graph demonstrating monthly rates of retinal vein occlusion attacks (per 100,000) by age from 1999 to 2003 in Taiwan.

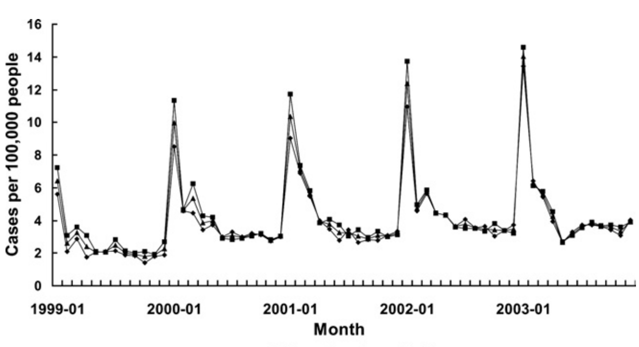

FIGURE 2. Graph demonstrating monthly rates of retinal vein occlusion attacks (per 100,000) by gender from 1999 to 2003 in Taiwan.

The monthly mean of retinal vein occlusion incidence was 0.89 per 100,000 persons in the 40 to 49 year range. This rate increased to 10.52 per 100,000 persons in the 70 years of age and older group. The monthly retinal vein occlusion incidence rates per 100,000 of the population ranged from a low of 1.78 in October 1999 to a high of 14.01 in January 2003, with a mean of 4.12 and a standard deviation of 2.37. The mean monthly retinal vein occlusion incidence rate was 4.31 for males and 3.91 for females.

• **SEASONALITY:** Spring occurs in Taiwan from March through May, summer from June through August, autumn from September through November, and winter from December through February. The seasonal variations in the monthly retinal vein occlusion rates for each gender group, each age group, and a combination of both gender groups are provided in Figures 1 and 2. It is evident from these two figures that the seasonal patterns in the monthly retinal vein occlusion rates were very similar for different age and gender groups, with the seasonal trends indicating a January peak. It also was noted that the top three months for monthly retinal vein occlusion incidence for the total sample were January, February, and March in each year during the five-year study period (with February being the second in two years and March being the second the other three years). The autoregressive integrated moving average test results for seasonality were found to be significant for each gender group, each age group, and for the entire sample (all $P < .001$).

As demonstrated in Tables 3 and 4, after adjustment for seasonality and trends, the autoregressive integrated moving average regression models indicated that the monthly retinal vein occlusion attack rates were positively and significantly associated with the month of January for each gender group, each age group, and for the entire sample (all $P < .001$). After adjustment for seasonality and trends, the month of November was negatively and significantly associated with the monthly retinal vein occlusion attack rates for the 60 to 69 years of age group and the 70 years and older group, both gender groups, and the entire sample (all $P < .05$). However, the month of November did not show significant association with the monthly retinal vein occlusion attack rates for the 40 to 49 years and 50 to 59 years groups (both $P > .05$). After adjustment for seasonality and trends, the month of December was associated

TABLE 3. Autoregressive Integrated Moving Average Analysis of Seasonal Effects on Monthly Retinal Vein Occlusion Attack Rates in Taiwan, by Age Group*

	Age (yrs)							
	40 to 49		50 to 59		60 to 69		≥ 70	
Independent Variables†	β	*t* value	β	*t* value	β	*t* value	β	*t* value
Intercept	7.957	0.26	142.204	2.18‡	65.697	0.38	104.300	0.37
AR1	0.921	17.93‖	0.831	21.12‖	0.707	5.75‖	0.757	8.58‖
MA1	−0.997	−9.54‖	−0.997	−17.58‖	−0.578	−3.06§	−0.997	−9.66‖
January	1.167	4.21‖	4.626	7.47‖	11.220	6.97‖	20.070	7.49‖
November	−0.146	−0.94	−0.954	−1.25	−2.280	−2.38‡	−4.599	−2.87§
December	−0.071	−0.56	−0.761	−0.83	−1.735	−1.36	−5.720	−2.72§
Trend	−0.001	−0.24	0.012	1.99	0.051	2.53‡	0.063	3.21§
AIC	−0.256		1.421		3.442		4.320	
Schwarz criterion (SC)	0.413		2.090		4.111		4.989	
R^2	0.858		0.952		0.939		0.954	

AIC = Akaike information criteria; AR1 = autoregressive, lag 1; MA1 = moving average, lag 1.
*Total sample number = 20,792.
†Reference month, July. Selection of the final parameters was based on the lowest AIC and SC.
‡$P < .05$.
§$P < .01$.
‖$P < .001$.

TABLE 4. Autoregressive Integrated Moving Average Analysis of Seasonal Effects on Monthly Retinal Vein Occlusion Attack Rates in Taiwan, by Gender

	Female		Male		Total	
Independent Variables†	β	*t* value	β	*t* value	β	*t* value
Intercept	54.040	0.54	2.954	0.03	56.329	0.61
AR1	0.652	4.97‖	0.825	15.67‖	0.631	5.68‖
MA1	−0.447	−2.20‡	−0.997	−11.57‖	−0.514	−2.83§
January	5.932	6.22‖	7.645	9.11‖	6.829	7.93‖
November	−1.174	−2.09‡	−1.615	−3.18§	−1.331	−2.63‡
December	−0.783	−0.11	−1.916	−2.89§	−1.432	−2.15‡
Trend	0.032	2.75§	0.015	2.12‡	0.028	3.05§
AIC	2.354		2.030		2.156	
Schwarz criterion (SC)	3.023		2.699		2.825	
R^2	0.930		0.965		0.952	

AIC = Akaike information criteria; AR1 = autoregressive, lag 1; MA1 = moving average, lag 1.
*Total sample number, 20,792.
†Reference month, July. Selection of the final parameters was based upon the lowest AIC and SC.
‡$P < .05$.
§$P < .01$.
‖$P < .001$.

negatively and significantly with the monthly retinal vein occlusion attack rates for the 70 years and older group, the male group, and the entire sample (all $P < .05$). However, the month of December did not show significant association with the monthly retinal vein occlusion attack rates for the 40 to 49 years, 50 to 59 years, and 60 to 69 years groups and the female group (all $P > .05$). Other months of the year (from February through October) did not have statistically significant association with the monthly retinal vein occlusion rates for the entire sample (all $P > .05$).

• **VISITS FOR NONRETINAL VEIN OCCLUSION BUT POSSIBLY RELATED DISEASES:** Figure 3 presents the number of monthly outpatient/emergency visits for non–retinal vein occlusion but possibly related diseases both individually and collectively (myocardial infarction/ischemic hear disease, hy-

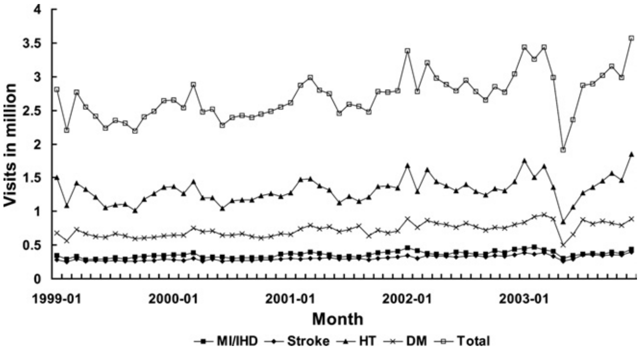

FIGURE 3. Graph demonstrating the number of monthly outpatient/emergency visits for principal diagnosis of non–retinal vein occlusion but possibly related diseases (including myocardial infarction/ischemic heart disease, hypertension, stroke, diabetes mellitus; in millions, for each disease individually or collectively) in Taiwan, from 1999 to 2003.

pertension, stroke, and diabetes mellitus) in Taiwan from 1999 through 2003. In this figure, there are no high-spiking peaks of visits for these diseases individually or collectively (as there are with the January peaks in Figures 1 and 2). It can be found in Figure 3 that the number of visits in January for these diseases was similar to number of visits in March in each year over the five-year study period.

DISCUSSION

OUR RESULTS ARE SIMILAR TO THOSE OF THE LAVIN AND Dhillon study, which demonstrated seasonal variations in CRVO incidence rates.[19] However, their study showed two peaks in the CRVO monthly incidence in London—during February and September—whereas the peak in the retinal vein occlusion incidence occurred consistently in January for each year in our study in Taiwan. Several factors may be involved in this difference, including the differences in the case ascertainment methods and differences in living conditions and climates between the two locations. A correlation was found in their study between the monthly temperature and monthly CRVO incidence rate ($r = -0.48$).

Our findings differ from those of Hayreh and associates study, which reported no seasonal variations in the onset of retinal vein occlusion.[20] In their study, the months were categorized into three subgroups according to temperature (cold from November to March, mild during April, May and October, and hot from June to September), and they found no association between ambient temperature and the retinal vein occlusion incidence. Malayan and associates study also found no seasonal patterns in retinal vein occlusion incidence.[21] A possible explanation for the discrepancies among the various studies may be that they relied on data from only a single hospital, or a few selected hospitals, and subpopulations of patients, each of which was not sufficiently representative to allow unequivocal conclusions.

Weather and season have long been recognized as an important triggering factor for various disorders, including stroke,[15,16] acute myocardial infarction,[17,18] etc.[24–27] Cold temperature is associated with increase in red blood cell counts, platelet counts, plasma cholesterol, fibrinogen and α-2 macroglobulin, and arterial blood pressure, as well as decrease in antithrombin 3.[28–31] Blood viscosity and plasma fraction of platelets begin to increase after cold exposure.[30] These effects of low temperature on blood coagulability and plasma viscosity may make the subjects more susceptible to acute thrombotic events. It is interesting to note in our study that peak incidence in retinal vein occlusion occurred in January in each year of the five-year study period. Concurrently, January also was the coldest or the second coldest month in each year in Taiwan during the study period (see Supplemental Figure 1 available at AJO.com).

A possible concern is that of misclassification of time of event and delay to diagnosis, a possible problem with smaller BRVO. It would be a problem if there was a selective seasonal diagnosis bias related to factors that result in patients being seen at some times of years for other non–retinal vein occlusion but possibly related events (e.g., myocardial infarction/ischemic heart disease, hypertension, stroke, and diabetes mellitus), when they tell their primary care doctor about a specific ocular symptoms they had experienced previously but did not come in to be treated for. To address this point, we present the number of monthly outpatient/emergency visits for these non–retinal vein occlusion but possibly related diseases in Taiwan from 1999 through 2003 in Figure 3. In this figure, there are no high-spiking peaks of visits for these diseases individually or collectively in the months of January and December (as with the January peaks of monthly retinal vein occlusion incidence in Figures 1 and 2). In addition, the number of visits in January for these diseases was close to the number for March in each year during the five-year study period. Although the incidences of acute myocardial infarction and acute stroke have been shown to be increased in winter,[15–18] these patients with acute events constituted only a small portion of the entire population with these diseases, including those in the recovery and chronic stages (most of the acute myocardial infarction or stroke patients were sent to the emergency service; the outpatient visit-to-emergency visit ratio was 35.7:1 for myocardial infarction/ischemic heart disease and 29.6:1 for stroke during the study period). Most of the patients with these diseases were followed up regularly by the physician over the entire year. The chances of being referred by their physician to an ophthalmologist therefore would be consistent over the entire year. Assuming the monthly incidence of retinal vein occlusion for January was similar to that for other months in the year (i.e., our observation of January peaks in monthly incidence of retinal vein occlusion in this study actually was not a true phenomenon) and given that the apparent January peak observed in our study was caused largely by the factors that the patients with these non–retinal vein occlusion but possibly related diseases were seen more frequently at certain times of the year, then it would be expected that the shape of the curves for the monthly number of visits for these related diseases would be similar to that of the curve representing the monthly incidence of retinal vein occlusion. However, it is evident by comparing Figure 2 with Figure 3 that this parallel in curve shapes does not exist. Therefore, the assumption that the monthly incidence of retinal vein occlusion for January is similar to that of other months is not true. That is, our observation of January peaks should be a true phenomenon and can not be explained by increased medical visits for other related diseases at certain times of the year.

Given the adequate number of ophthalmologists on the relatively small island of Taiwan (ophthalmologist-to-population ratio, 1:14,375; compared with 1:23,523 in the United Kingdom[32]), negligible barriers to medical access (the National Health Insurance System in Taiwan allows patients to visit any ophthalmology clinic or the department of ophthalmology of any hospital freely without referral by a general practitioner) and the severity of retinal vein occlusion disorder, we believe most patients with retinal vein occlusion would search for medical help soon after disease onset. The interval between retinal vein occlusion occurrence and the patients' presentation for examination in our study would be similar to or shorter than that of previous hospital-based studies.[19–21] In these previous studies, the patients likewise looked for medical help after they noted the onset of the retinal vein occlusion.

In addition, the people in Taiwan declare income taxes each May for incomes and expenditures of the previous year. Medical services were provided at the same price (a price is instituted by the National Health Insurance Bureau of the government) over the course of the year. Consequently, there is no tax-related or financial reason for people to be more likely to come to the clinic or hospital in January. We present the number of monthly outpatient/emergency visits (including visits for ophthalmic and nonophthalmic diseases together) in Taiwan from 1999 through 2003 in Supplemental Figure 2 (available at AJO.com). It is evident that January was not the month with highest number of visits overall for each year of the study period.

There are, nevertheless, several limitations of this study. First, some patients may not seek direct medical help. This may occur because of a lack of recognition of the severity of the visual loss attributable to retinal vein occlusion, particularly patients who are already visually compromised. However, this limitation also would be present in hospital-based studies. Second, a substantial number of BRVOs are incidental findings during dilated fundus examination, and this may result in a discrepancy between the date of diagnosis and date of disease onset. However, the number of these subclinical BRVOs would dilute or mask any real cyclical pattern of retinal vein occlusion occurrence. In our study, retinal vein occlusion incidence showed a strong cyclical pattern even in the presence of such diluting factors. Therefore, our observation of a cyclical pattern in retinal vein occlusion occurrence is a real phenomenon. Third, the ICD coding may be a source of underestimation of the retinal vein occlusion incidence. In this study, we used the ICD-9-CM diagnosis code 362.35 (CRVO) as the definition for CRVO and the diagnosis code 362.36 (venous tributary (branch) occlusion) as the definition for BRVO, with these two codes comprising retinal vein occlusion as a whole. However, because this was a retrospective study and the diagnosis codes were determined by a variety of doctors, we have reason to believe that some of the CRVO and BRVO cases may have been given one of the more nonspecific diagnosis codes, including 362.3 (retinal vascular occlusion) or 362.30 (retinal vascular occlusion, unspecified). However, such factors are unlikely to explain our finding of seasonality in the retinal vein occlusion incidence, because less specific diagnoses would be expected to produce a much more constant error. Our examination of seasonality in the collective incidences of diagnosis codes 362.3 (retinal vascular occlusion), 362.30 (retinal vascular occlusion unspecified), 362.35 (CRVO), and 362.36 (venous tributary (branch) occlusion) led to identical conclusions, that is, that there were significant seasonal variations and constant peaks in each January (data not shown) in the collective incidences of these diagnosis codes. Finally, this study has been undertaken in a subtropical environment, a fact which may restrict somewhat the generalizability of the findings to other locations with distinctly different environmental characteristics.

In summary, this nationwide population-based study has demonstrated significant seasonal variations in retinal vein occlusion incidence, with a clear peak in January. These findings suggest that, in addition to the well-recognized endogenous risk factors, exogenous environmental factors also may be important in the occurrence of retinal vein occlusion. Similar studies elsewhere in the world are expected to see if our data can be replicated and to help clarify the seasonality of retinal vein occlusive diseases.

THE AUTHORS INDICATE NO FINANCIAL SUPPORT OR FINANCIAL CONFLICT OF INTEREST. INVOLVED IN DESIGN AND conduct of study (J.-D.H., H.-C.L.); collection (C.-Y.T., H.-C.L.), management (J.-D.H., S.-W.L., H.-C.L.), analysis and interpretation of the data (J.-D.H., R.J.-F.T., H.-C.L.); and preparation (J.-D.H., C.-Y.T., H.-C.L.), review (J.-D.H., C.-Y.T., S.-W.L., H.-C.L.), and approval of the manuscript (J.-D.H., C.-Y.T., S.-W.L., R.J.-F.T., H.-C.L.). The Institutional Review Board of Taipei Medical University Hospital waived the need for approval for this study because the Taiwan National Health Insurance Research Database (NHIRD) contains only deidentified secondary data and is published by the National Health Research Institute of the government for research purposes. This study adhered to the Declaration of Helsinki and all laws in Taiwan.

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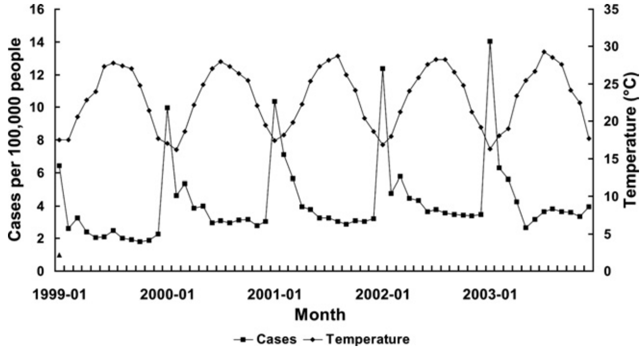
Biosketch

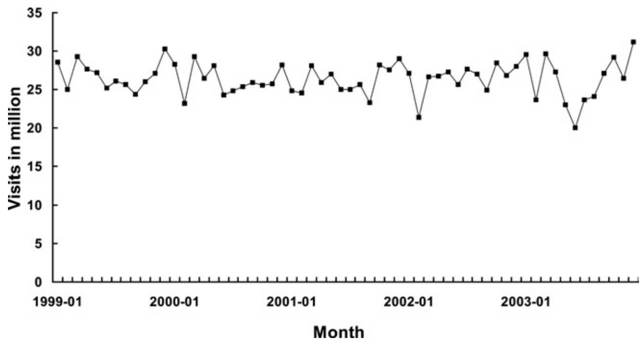
Jau-Der Ho, MD, PhD, completed medical school from the National Taiwan University (NTU), and ophthalmology training at NTU Hospital. He received his PhD degree from Chang-Gung University, Taiwan. Dr Ho is a subspecialist in vitreoretinal diseases, cataract, and vitreoretinal surgery. His research interests include retinal cell biology and ocular pharmacology. Dr Ho is currently an Assistant Professor and Chair of the Department of Ophthalmology, Taipei Medical University Hospital of Taipei, Taiwan.

Biosketch

Shiow-Wen Liou, MD, PhD, graduated from Medical School of the National Taiwan University (NTU), and completed ophthalmology training at NTU Hospital, Taipei, Taiwan. She received her PhD degree at Dokkyo Medical University in Japan and MHS degree from Johns Hopkins University, Baltimore, Maryland. Dr Liou is a subspecialist in cataract, strabismus, and oculoplastic surgery. Dr Liou currently serves as the Superintendent of Zhongxing branch, Taipei City Hospital, Taiwan and Professor of Ophthalmology in Taipei Medical University.



SUPPLEMENTAL FIGURE 1. Monthly rates of retinal vein occlusion attacks (per 100,000) and monthly average ambient temperature in Taiwan, from 1999 to 2003.



SUPPLEMENTAL FIGURE 2. The number of monthly outpatient/emergency visits (in millions, for both ophthalmic and nonophthalmic diseases) in Taiwan, from 1999 to 2003.