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Age, Gender, and Laterality of Retinal Vascular Occlusion:

A Retrospective Study from the IRIS[®] Registry

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Abstract

Purpose: Retinal vascular occlusion is a leading cause of profound irreversible visual loss, but the understanding of the disease is insufficient. We systematically investigated the age, gender, and laterality at the onset of retinal artery occlusion (RAO) and retinal vein occlusion (RVO) in the IRIS[®] Registry (Intelligent Research in Sight).

Design: A retrospective registry cohort.

Participants: Retinal vascular occlusion cases participating in the IRIS Registry.

Methods: All cases diagnosed as retinal vascular occlusion in the IRIS Registry between 2013 and 2017 were included. Cases with unspecified gender or laterality were excluded when conducting the relevant analyses. Cases were categorized based on diagnosis codes into RAO,

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with subtypes transient retinal artery occlusion (TRAO), partial retinal artery occlusion (PRAO), branch retinal artery occlusion (BRAO), and central retinal artery occlusion (CRAO), and into RVO, with subtypes venous engorgement (VE), branch retinal vein occlusion (BRVO), and central retinal vein occlusion (CRVO). Age was evaluated as a categorical variable (5-year increments). We investigated the association of age, gender, and laterality with the onset frequency of retinal vascular occlusion subtypes.

Main outcome measures: The frequency of onset of RAO and RVO subtypes by age, gender and laterality.

Results: A total of 1,251,476 retinal vascular occlusion cases were included, 23.8% of which were RAO, while 76.2% were RVO. 1,248,656 and 798,089 cases were selected for analysis relevant to gender and laterality, respectively. The onset frequency of all subtypes increased with age. PRAO, BRAO, CRAO, and CRVO presented more frequently in men (53.5%, 51.3%, 52.6%, 50.4%), while TRAO, VE, and BRVO presented more frequently in women (54.9%, 56.0%, 54.5%). BRVO and all RAO subtypes showed a right-eye onset preference (BRVO 51.0%, TRAO 51.7%, PRAO 54.4%, BRAO 53.5%, CRAO 53.4%), while VE and CRVO exhibited a left-eye onset preference (VE 53.3%, CRVO 50.9%).

Conclusions: While retinal vascular occlusion incidence increases with age regardless of subtypes, we found various subtype-specific disease onset differences related to gender and, in particular, ocular laterality. These findings may improve understanding of the specific etiology of retinal vascular occlusions of different subtypes and their relationship with structural and anatomic asymmetries of the vascular system.

Keywords

retinal vascular occlusion; retinal artery occlusion; retinal vein occlusion; laterality; age; gender; big data; epidemiology; demographics

Introduction

Retinal vascular occlusion, one of the leading causes of profound irreversible visual loss, is comprised of a group of retinopathies characterized by blood flow blocked in arteries or veins. According to the vessels affected, retinal vascular occlusions can be categorized into retinal artery occlusion (RAO) and retinal vein occlusion (RVO). Collectively, retinal vascular occlusion (both RAO and RVO) is one of the most common causes of visual disability in the world's middle-aged and elderly population.^{1,2}

The American Academy of Ophthalmology IRIS[®] Registry (Intelligent Research in Sight) is an extensive, comprehensive clinical eye disease data registry.^{3,4} It consists of data from more than 349 million patient visits contributed by more than 18,000 contracted healthcare providers in the United States (as of September 1, 2020). The database was launched on March 24, 2014, and continues to grow each day.⁵ The IRIS Registry platform provides a large-scale glimpse into eye disease trends, features, and real-world information such as patients' diagnoses, treatment choices, and outcomes.³⁻⁹ By compiling visit and surgical history from a diverse set of patients across the United States, the IRIS Registry dataset allows further study of existing clinical assumptions using a large dataset.

RAO cases in the IRIS Registry can be sub-classified according to diagnosis codes into central retinal artery occlusion (CRAO), branch retinal arterial occlusion (BRAO), partial retinal arterial occlusion (PRAO), and transient retinal arterial occlusion (TRAO). PRAO indicates the incomplete disruption of blood flow,^{12,13} and in clinical practice, TRAO is commonly referred to as transient ischemic attack. Published estimates suggest that the incidence rates are 1.64 per 100,000 person-years for CRAO, 4.99 per 100,000 person-years for BRAO, and 6.63 per 100,000 person-years for RAO.^{10,11}

RVO cases in the IRIS Registry can be sub-classified according to diagnostic code into central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), and venous engorgement (VE). Epidemiological analyses reveal that the global prevalence of RVO, BRVO, and CRVO reached 28.06 million (0.77%), 23.38 million (0.64%), and 4.67 million (0.13%) respectively in people aged 30–89 in 2015, while the pooled five- and ten-year cumulative incidences of RVO were 0.86% and 1.63%, respectively.¹² Compared to RAO, the incidence rate for RVO is higher, with 48.31 per 100,000 person-years.¹³ Clearly, the widespread prevalence of RVO is of global significance.

Previous studies have investigated the etiology, demographic characteristics, and risk factors of retinal vascular occlusion. The etiology of RAO is embolus, thrombus, and less commonly arteritis, leading to blockage of the central retinal artery or one of its branches; blockage can be permanent in the case of CRAO, BRAO, and PRAO or transient in the case of TRAO.^{14–17} Identified risk factors for RAO include hypertension,^{18,19} hypercholesterolemia,^{17,19} carotid artery disease,^{20,21} cardiac disease,^{16,22} heart attack history,^{18,23} stroke history,^{15,21} and smoking.^{17,24}

The etiology of CRVO is thought to be occlusion of the central retinal vein at or proximal to the lamina cribrosa, due to thrombosis.²⁵ Abnormalities in blood clotting or blood viscosity due to a variety of systemic diseases may contribute to CRVO in some cases.^{26–28} Known disease associations with CRVO are systemic arterial hypertension, diabetes mellitus, and open-angle glaucoma.²⁹ Oral contraceptive and diuretic use have also been identified as risk factors.³⁰ The etiology of BRVO is thought to be a thrombus at arteriovenous crossings. Risk factors for BRVO are systemic arterial hypertension, cardiovascular disease, a history of glaucoma³¹ and advanced age.^{32–34}

Of note, some studies found that RVO^{34,35} and RAO³⁶ occurred more frequently in men while others report no difference between men and women, and so gender predilection is still uncertain.^{23,32,37} Few studies have compared the eye laterality at the onset of any subtype of retinal vascular occlusion.

Knowledge of laterality differences in vascular occlusion will provide a more comprehensive understanding of these disease processes' pathogenesis and enable further studies to advance the diagnosis and treatment. Structural and anatomic asymmetry of the aortic arch may explain a right-eye laterality preference for RAO. Emboli causing RAO can originate from plaques within the blood vessels, often the carotid arteries, or within the heart.^{16,17} The central retinal artery is a branch of the ophthalmic artery, which gets its blood supply from the common carotid artery. However, the origin of right and left common carotid arteries are

different. The right common carotid artery is a branch of the brachiocephalic trunk, while the left common carotid artery originates directly from the aortic arch. The brachiocephalic trunk is the first orifice of the aortic arch. Thus, emboli in the blood that flows out of the left ventricle will reach the brachiocephalic trunk first. As a result, emboli may have a higher chance of entering the right common carotid artery through the brachiocephalic trunk than entering the left common carotid artery in cases when the embolus originates from the heart.³⁸ A 416-patient retrospective study reported a tendency of predominance in men and right-eye onset in RAO patients, but the gender and laterality differences were not statistically significant.³⁹ In this paper, we report our analyses of the vast amount of data available in the IRIS Registry to examine gender and laterality in all subtypes of vascular occlusion. We aim to investigate previously held but unproven assumptions about the pathophysiology of vascular occlusion, specifically the effects of gender, age, and laterality on disease onset.

Methods

Data source

The IRIS Registry, as described above, was used as the data source in this analysis. The version published by the IRIS Registry on 07/26/2019 was accessed on 12/12/2019 and used to select cases for this study. The IRIS Registry is maintained by the American Academy of Ophthalmology and contains integrated data from numerous different electronic health record (EHR) systems provided by contracted healthcare providers.⁴⁰ Patients' information is de-identified during the data collection procedure, and only fully de-identified data were used in our study. As such, researchers have no access to identifying information for any particular patient. According to Partners Human Research Committee (PHRC) Policy *Definition of Human-Subjects Research*, the institutional review board of Massachusetts Eye and Ear classified this study as exempt because data were de-identified, which implied that the patients' informed consent to this study was not necessary. This study adhered to the Declaration of Helsinki

Selection criteria and measurements

All patients with records between January 1, 2013, and December 31, 2017, in the IRIS Registry, who were diagnosed with TRAO, PRAO, BRAO, CRAO, VE, BRVO, and CRVO on the first visit, were included in the data analyses.

Diagnoses were stored as International Classification of Diseases, 9th revision and 10th revision (ICD-9 and ICD-10) codes in the IRIS Registry. They were identified and paired according to the description. That is, cases with codes H34.0*/362.34 were identified as TRAO, with codes H34.21*/362.33 as PRAO, with codes H34.23*/362.32 as BRAO, with codes H34.1*/362.31 as CRAO, with codes H34.82*/362.37 as VE, with codes H34.83*/362.36 as BRVO, and with codes H34.81*/362.35 as CRVO, in ICD-10/ICD-9 codes respectively, where an asterisk, "*", indicates any number of any digits that may follow in the code from that point onward, i.e., it includes all possible "subcodes" of the respective base code.

We determined laterality for our analysis by integrating documentation from the IRIS Registry EHR-based laterality variable along with laterality based on diagnosis codes (if specified). We classified vascular occlusions as “bilateral” onset either when “bilateral” was specified in the diagnosis or when the disease was diagnosed separately for the right and left eye within the same calendar year of onset. This definition was based on the granularity of date only to year in the IRIS version used for this analysis. Our data analysis combined two diagnostic systems (ICD-9 and ICD-10 codes). While ICD-9 codes do not consider laterality, ICD-10 codes allow for the decoding of laterality within the diagnostic code. As this could have introduced different tendencies in reporting vs. not reporting laterality between the two systems, we additionally performed our main data analyses and compared the results in ICD-10 and ICD-9 codes separately and found little difference (SI Table 1–2, supplementary files are available at www.aaojournal.org), which supported our use of data from cases based on both ICD-10 and ICD-9 codes.

The study focused on the age, gender (men and women), and laterality (right eye, left eye, and both eyes) at the onset of the disease. There are two dates relevant to clinical diagnoses in the IRIS Registry. “Documentation year” specifies that a diagnosis was documented in the electronic medical record of the respective year. Typically, from the first time of the diagnosis forward, the diseases were reported every year in the database. “Onset year” explicitly refers to the year of the first diagnosis. While the “onset year” entry was not always available, each diagnostic entry contained at least one documentation year, and the first documentation year of disease is supposed to coincide with the disease onset year. Cases where the onset year was later than the documentation year were excluded. If an onset year was explicitly reported, it was selected for data analysis. If no onset year for the respective eye was explicitly specified, we selected the earliest documentation year as the onset year. Age was defined as the time between onset year/documentation year and year of birth. Age was categorized into five-year intervals from age 0 to age 84 and 85 when cases were 85 years old or older. Gender was categorized in the IRIS Registry as male, female, and unspecified. The entire set of IRIS Registry diagnoses included eye-related codes within ICD-9 and ICD-10.

Patients with missing or unspecified subtype diagnosis information (3.0%) were excluded from the data analysis. Cases without specified gender (0.2%) or laterality (35.1%) information were excluded when the relevant analyses of gender or laterality were conducted. Details of the exclusion process are presented in Figure 1. The baseline characteristics and the comparisons of selected and excluded cases are described in the supplementary material.

Statistical analysis

The overall comparisons of interest were: the association of onset frequency and age, the association of onset frequency and gender, the correlation between gender and age, the association of onset frequency and laterality, and the correlation between laterality and age. We present all parameters with both the number of cases and corresponding percentages. We use a Spearman test to test the correlation between onset and age, and between onset laterality and age. We use a binomial test to compare the onset proportion by gender

(null hypothesis: the proportion of each gender was 0.5), unilateral onset proportion (null hypothesis: the proportion of unilateral onset of each subtype was that of the entire set of IRIS Registry), and onset proportion by laterality (only for unilateral onset cases, null hypothesis: the proportion of right-eye or left-eye onset was 0.5). We use a Z test to compare the proportion differences between men and women, between unilateral and bilateral onset, and between right-eye and left-eye onset. All procedures were performed in R software version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). $P < 0.01$ was considered statistically significant. A 99% confidence interval (99% CI) and the odds ratio (OR) were given.

Results

Baseline Description

A total of 1,289,836 cases of retinal vascular occlusion identified were included from the entire set of IRIS Registry diagnoses (299,385,279 cases with ophthalmic diseases) as of December 31, 2017. We defined the date of onset by the date of the first visit at which a new diagnosis was given. The prevalence of retinal vascular occlusion among the entire set of IRIS Registry diagnoses, as defined by the date of onset, was 4.31%. According to the inclusion and exclusion criteria, after exclusions of 38,360 cases without specified subtype diagnosis, 1,251,476 cases of retinal vascular occlusion remained for analysis (Figure 1). The baseline characteristics overall and for each retinal vascular occlusion subtype are described in Table 1. According to their diagnosis, patients were classified into seven subtypes, with subtype frequency ranging from 21,075 for VE to 573,880 for BRVO. RAO cases made up 23.8% of retinal vascular occlusion cases (4.9% for TRAO, 4.5% for PRAO, 8.3% for BRAO, and 6.1% for CRAO), while RVO composed 76.2% of cases (1.7% for VE, 45.9% for BRVO, 28.6% for CRVO). The population distribution according to age intervals was presented in Figure 2 (overall view of the entire set of IRIS diagnoses, retinal vascular occlusion, RAO, and RVO), Figure 3 (subtypes of RAO), and Figure 4 (subtypes of RVO). As the gender and laterality information of some cases was unspecified, we excluded those cases when analyzing gender and laterality. The number of cases selected and excluded and exclusion criteria at each step are described in Figure 1. The baseline characteristics of the selected cases are described before each analysis.

Association of Age with Retinal Vascular Occlusion Onset

For the total included retinal vascular occlusion population, the frequency of onset rose with increasing age between 0 to 84 years old (Table 1). Only 0.5% (0.3% to 2.0% by subtype) of cases were less than 25 years old, 2.7% (1.6% to 6.0% by subtype) of cases were between 25 and 45 years old, and 24.3% (22.2% to 32.9% by subtype) of cases were between 45 and 65 years old. Patients aged between 65 and 85 years old composed 70.3% (59.3% to 74.0% by subtype) of cases, which were the largest component. The percentage of patients equal to or above 85 years old was 2.2% (0.9% to 2.5% by subtype) due to the low enrollment of the very elderly patients in the IRIS Registry platform; the same percentage in the entire set of IRIS Registry diagnoses was 1.0%. The Spearman correlation coefficients and 99% CI for the onset of each subtype with age are given in SI Table 3; they range from 0.82 to 0.93 by subtype and demonstrate high positive correlations between subtypes of retinal vascular

occlusion and age of onset; the correlation of the entire set of IRIS Registry diagnosis with age is 0.64.

Association of Gender with Retinal Vascular Occlusion Onset

A total of 1,248,656 cases were selected for gender-related analysis after 2,820 (0.2%) cases without specified gender were excluded. The baseline characteristics and comparison of selected and excluded cases were presented in SI Table 4.

The percentages of men and women among selected retinal vascular occlusion cases were 48.2% and 51.8%, respectively. PRAO, BRAO, CRAO, CRVO were more frequent among men, while TRAO, VE, and BRVO were more frequent among women. The frequency differences between men and women in each subtype were 7.0%, 2.6%, 5.3%, 0.9% for PRAO, BRAO, CRAO, CRVO, and -9.8%, -12.0%, -8.9% for TRAO, VE, BRVO (Table 2, $p < 0.0001$ for each subtype).

The spearman correlation of percentages of men with age was calculated to investigate the association of age and gender differences (SI Table 5). Only the gender distribution of RAO was slightly associated with age. The trends in the gender distribution of other subtypes (TRAO, PRAO, BRAO, CRAO, RVO, VE, BRVO, and CRVO) were not significantly correlated with the age category. Details are presented for the proportion of men and women with each subtype across 5-year age categories (SI Table 6). The frequency of all vascular occlusion subtypes increased with age, overall and separately for men and women.

Association of Laterality with Retinal Vascular Occlusion Onset

For analyses relevant to laterality, we excluded 453,387 cases without specified laterality information. Thus, 798,089 cases were selected. The baseline characteristics and comparison of the cases with/without specified laterality were presented in SI Table 7.

Unilateral onset was significantly more frequent among retinal vascular occlusion cases (90.5%) than among the entire set of all IRIS Registry diagnoses (32.3%). The same trend was observed in each subtype ($P < 0.0001$ for each subtype with 99% CI given in Table 3). As for the association of age and laterality preference by subtype, the Spearman test showed a positive correlation between unilateral onset with age in all subtypes except PRAO and VE, which displayed no significant correlation (SI Table 8 and the details in SI Table 9). The Spearman correlation coefficients ranged from 0.66 to 0.97.

We examined the right-eye and left-eye differences among unilateral onset cases in each subtype of retinal vascular occlusion (Table 4). For BRVO and all four subtypes of RAO, right-eye onset was more frequent than left-eye onset. For VE and CRVO, onset was more frequent in the left eye than the right eye ($p < 0.0001$ for each of these seven subtypes). To investigate the association of age and right eye versus left eye onset by subtype, we calculated the percentages with right-eye onset among men, women, and cases with unspecified gender by 5-year age intervals (SI Figure 1). The Spearman correlation coefficients ranged from -0.03 to 0.57 between right-eye onset frequency and age, which did not suggest a meaningful correlation (SI Table 8).

Discussion

In this study, we used the IRIS Registry, a large national database. In accordance with previous publications,^{10,11,13} there was a significantly higher rate of venous occlusions than arterial occlusions in this dataset. We observed a positive correlation between onset frequency and age in each subtype. The onset differences related to gender and laterality were heterogeneous in each subtype.

Age is a well-known risk factor of retinal vascular occlusion; disease onset increased with age for all subtypes of retinal vascular occlusion (SI Table 3 and Figure 2–4).³² This trend may be due to worsening cardiovascular disease with age;^{18,30} unfortunately, we do not currently have access to co-morbidities in the IRIS Registry, but this area warrants future study.

Previous studies have suggested a predominance for RVO and RAO in men.^{34–36} In our study, there were slightly more women in TRAO, VE, and BRVO, and more men in PRAO, BRAO, CRAO, and CRVO (Table 2). The gender differences in all subtypes were significant (all p values < 0.0001). Past studies have suggested that venous thromboembolism occurs more commonly in women under age 55 because of pregnancy, postpartum status, and oral contraceptive medication. But in older populations, cases among men tend to be more common, perhaps due to cardiovascular risk factors.^{41,42} We observed this trend (SI Table 6) even though we found no significant correlation between age and percentages of men (SI Table 5). The proportion of women trended up in older age categories, which may be related to the longevity of women.⁴³ Again, information on medication use and co-morbidities are not currently available in the IRIS Registry, but when added, will further elucidate the relationships between retinal vascular occlusion and gender.

Unilateral onset was more common than bilateral onset in all retinal vascular occlusion subtypes, except for VE. Of note, all subtypes, including VE, had a significantly higher unilateral onset rate than the entire set of IRIS Registry (Table 3). Given the pathophysiology of all arterial occlusions, BRVO, and CRVO, it is not surprising that a unilateral onset is most frequent. By comparison, the VE more commonly presented bilaterally (VE 60.1% vs. retinal vascular occlusion 9.5% for bilateral presentation). As VE indicates the incipient or partial occlusion of retinal veins, which could be asymptomatic and latent, doctors may be inclined to recognize the structural changes in both eyes and make a bilateral diagnosis simultaneously. Bilateral presentation is consistent with the known etiology of VE as a manifestation of systemic diseases, such as hyperviscosity syndrome.⁴⁴

Eye laterality onset difference in retinal vascular occlusion has not been comprehensively analyzed in the past. Our analyses demonstrate a left-eye preference in most subtypes of RVO except BRVO, as well as a right-eye preference in BRVO and all four subtypes of RAO (Table 4). To our knowledge, our study is the first to demonstrate a laterality deviation in all subtypes of retinal vascular occlusion. Arterial occlusions are frequently caused by emboli, which can arise from blood vessel walls or cardiac valves. Given the different anatomy of the vasculature leading to the central retinal arteries,³⁸ there is a pathophysiologic reason to expect that arterial occlusions would present more commonly in the right eye, as the

emboli from the heart would be more likely to block the right central retinal artery, in agreement with our findings of a right-eye preference for all arterial occlusions. Of course, it is essential to consider alternative explanations for this observation; in particular, most people are right-eye dominant, leading to reporting bias of right-eye disease. If right-eye bias were the explanation, one would expect it to be apparent for venous occlusion as well, but it was not.

Although there was a statistically significant left-eye preference for BRVO and right-eye preference for CRVO, there is no clear pathologic explanation for this difference. Thrombus formation would be expected to develop unilaterally but in each eye with a similar frequency. Notably, the right-eye preference of BRVO and the left-eye preference of CRVO were only 51.0% and 50.9%, respectively. By comparison, other etiologies demonstrated an approximately 3–8% difference in preference between right and left eye. This slight difference for venous occlusion may not be clinically significant.

It is known that the embolic etiology of stroke (cardiac versus vascular) differs among age groups.⁴⁵ We observed a positive correlation between age and unilateral onset in all subtypes except PRAO and VE (SI Table 8 and 9). Younger patients may have particular risk factors, such as coagulation abnormalities, leading to the early onset of retinal vascular occlusion in both eyes.³⁷ However, we found no correlation between age and right-eye onset in all subtypes of vascular occlusion, suggesting that if the vascular anatomy does account for the laterality difference in arterial occlusion onset overall, that right-eye and left-eye difference does not change with age.

There were some limitations to this study. The results rely on accurate coding of ICD-9/ICD-10 diagnoses, documented onset age, gender, and onset laterality. Patients visiting different institutions could cause duplication of diagnoses. However, the ICD codes are related to the insurance reimbursement claims and of high-level accuracy. As we only analyzed the principal diagnosis, most cases included were unique. Based on the large number of cases, the imprecision in coding and documentation can be slight and neglectable.

The IRIS Registry platform aggregates the collection, arrangement, and de-identification of EHR information from more than 18,000 healthcare providers. Due to the size of the Registry, there is a delay in the release of data. At the time of the data analysis, we only had access to the 2017 version of the database and could not include later cases.

In addition, we were unable to associate systemic measurements or other co-morbidities with diagnosis due to the current limitations of the IRIS Registry data set. An additional analysis that combines systemic and ophthalmic disease would be beneficial for a better understanding of retinal vascular occlusions. Similarly, medication information was not available; future analysis using medication data would further inform our findings.

Another potential limitation arises from the large number of cases with unreported eye laterality. It was the most frequent cause for excluding cases from our laterality-relevant analyses (SI Table 7). The cases with unspecified laterality accounted for 53.8% of cases in the entire set of IRIS Registry, and 36.2% of cases in retinal vascular occlusive diseases, which was lower than that in the entire set of IRIS Registry except for TRAO. As TRAO is a

RVO	retinal vein occlusion
IRIS Registry	Intelligent Research in Sight Registry
TRAO	transient retinal artery occlusion
PRAO	partial retinal artery occlusion
BRAO	branch retinal artery occlusion
CRAO	central retinal artery occlusion
VE	venous engorgement
BRVO	branch retinal vein occlusion
CRVO	central retinal vein occlusion
EHR	electronic health record
HIPAA	Health Insurance Portability and Accountability Act
ICD-9	International Classification of Diseases, 9th revision
ICD-10	International Classification of Diseases, 10th revision
99% CI	99% confidence interval
OR	odds ratio

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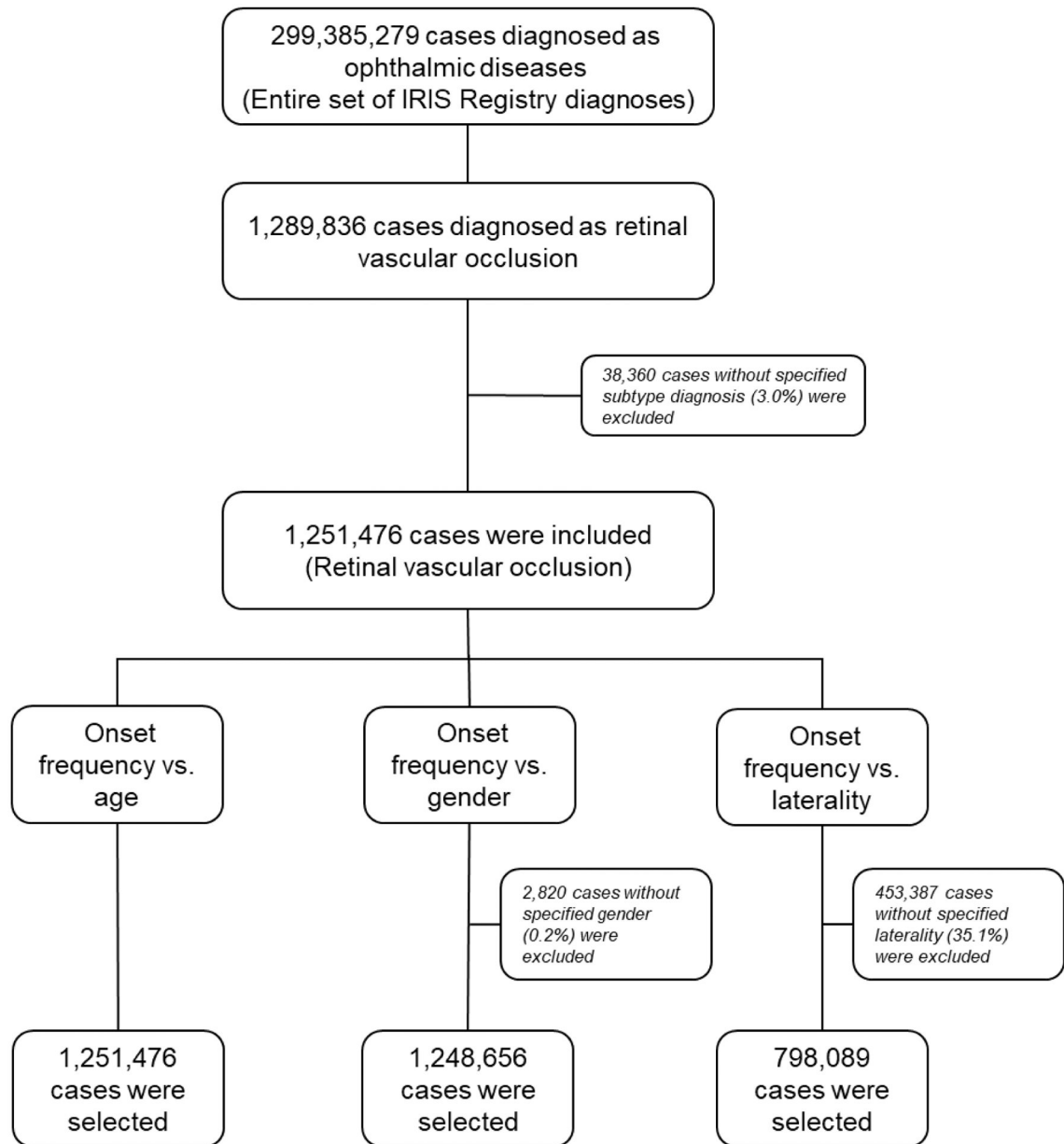


Figure 1. Selection of cases for analysis.

The number of cases retrieved from the entire Intelligent Research in Sight (IRIS) Registry database and included for analyses. The percentages of excluded cases were based on the 1,289,836 cases diagnosed with retinal vascular occlusion.

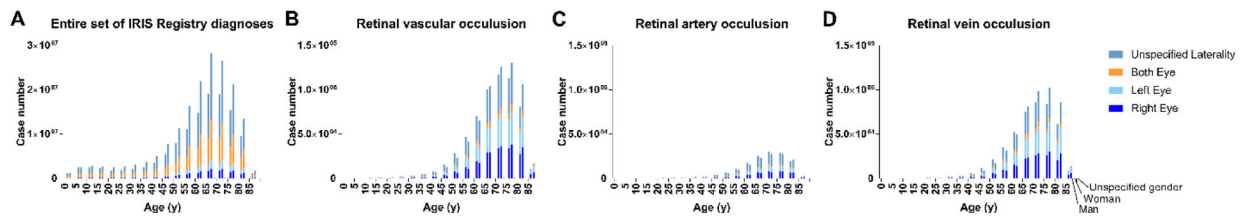


Figure 2. Distribution of the number of included cases by age, gender, and laterality at onset. Distribution of numbers of cases by age, gender and laterality at first diagnosis. The numbers of men, women, and unspecified gender cases are presented inline in each age category. Each bar shows the cumulative case numbers of right, left, both, and unspecified eye at onset. A. The entire set of Intelligent Research in Sight (IRIS) Registry diagnoses (y-axis 200 times larger than other plots). B. Diagnoses of retinal vascular occlusions. C. Diagnoses of retinal artery occlusions. D. Diagnoses of retinal vein occlusions.

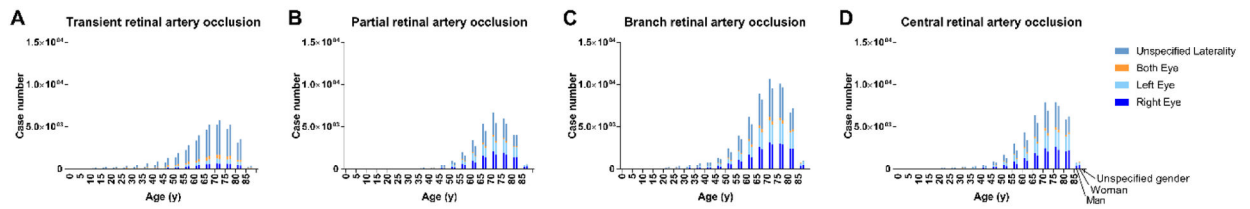


Figure 3. Distribution of the number of included cases of retinal artery occlusion by subtype, age, gender, and laterality at onset.

Distribution of numbers of cases by age and gender at first diagnosis. The numbers of men, women, and unspecified gender cases are presented inline in each age category. Each bar shows the cumulative case number of right, left, both, and unspecified eye at onset. A. Transient retinal artery occlusion. B. Partial retinal artery occlusion. C. Branch retinal artery occlusion. D. Central retinal artery occlusion.

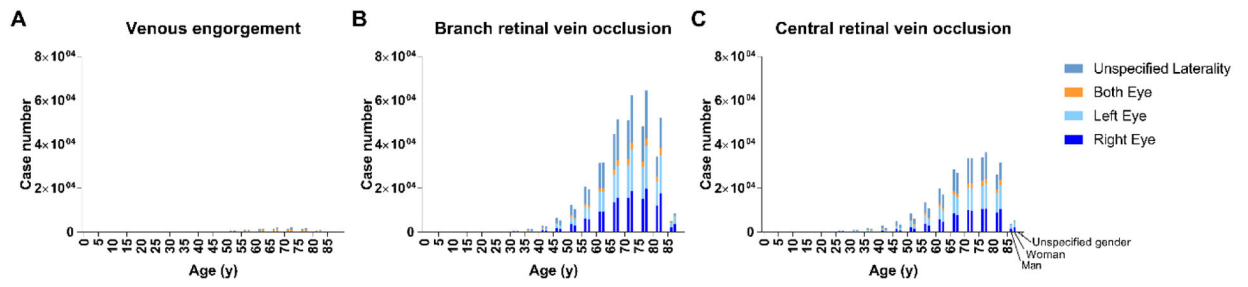


Figure 4. Distribution of the number of included cases of retinal vein occlusion by subtype, age, gender, and laterality at onset.

Distribution of numbers of cases by age and gender at first diagnosis. The numbers of men, women, and unspecified gender cases are presented inline in each age category. Each bar shows the cumulative case number of right, left, both, and unspecified eye at onset. A. Venous engorgement. B. Branch retinal vein occlusion. C. Central retinal vein occlusion.

Table 1.

The distribution of baseline characteristics of cases of retinal vascular occlusion selected for analysis.

	RAO				RAO	RVO			RVO	Retinal vascular occlusion	Entire set of IRIS Registry diagnoses
	TRAO	PRAO	BRAO	CRAO		VE	BRVO	CRVO			
n (% ^a)	61,241 (4.9)	56,133 (4.5)	103,942 (8.3)	76,268 (6.1)	297,584 (23.8)	21,075 (1.7)	573,880 (45.9)	358,937 (28.6)	953,892 (76.2)	1,251,476 (100.0)	299,385,279
Age											
0–25 (% ^b)	1,230 (2.0)	160 (0.3)	784 (0.8)	567 (0.7)	2,741 (0.9)	288 (1.4)	1,405 (0.3)	1,725 (0.5)	3,418 (0.4)	6,159 (0.5)	22,267,552 (7.4)
25–45 (% ^b)	3,701 (6.0)	921 (1.6)	3,987 (3.8)	2,219 (2.9)	10,828 (3.7)	1,164 (5.5)	10,605 (1.8)	11,433 (3.2)	23,202 (2.4)	34,030 (2.7)	24,628,180 (8.2)
45–65 (% ^b)	17,956 (29.3)	12,478 (22.2)	26,140 (25.1)	17,587 (23.1)	74,161 (24.9)	6,944 (32.9)	138,374 (24.1)	84,738 (23.6)	230,056 (24.1)	304,217 (24.3)	96,890,436 (32.4)
65–85 (% ^b)	37,715 (61.6)	41,505 (74.0)	71,292 (68.6)	54,282 (71.2)	204,794 (68.8)	12,490 (59.3)	410,171 (71.5)	251,985 (70.2)	674,646 (70.7)	879,440 (70.3)	152,780,390 (51.0)
85 (% ^b)	639 (1.1)	1,069 (1.9)	1,739 (1.7)	1,613 (2.1)	5,060 (1.7)	189 (0.9)	13,325 (2.3)	9,056 (2.5)	22,570 (2.4)	27,630 (2.2)	2,818,721 (1.0)
Gender											
Men (% ^b)	27,550 (45.0)	29,964 (53.4)	53,217 (51.2)	40,036 (52.5)	150,767 (50.7)	9,256 (43.9)	260,796 (45.4)	180,570 (50.3)	450,622 (47.3)	601,389 (48.1)	123,672,549 (41.3)
Women (% ^b)	33,539 (54.8)	26,063 (46.4)	50,492 (48.6)	36,026 (47.2)	146,120 (49.1)	11,788 (55.9)	311,885 (54.4)	177,474 (49.4)	501,147 (52.5)	647,267 (51.7)	175,061,945 (58.5)
Unspecified (% ^b)	152 (0.2)	106 (0.2)	233 (0.2)	206 (0.3)	697 (0.2)	31 (0.2)	1,199 (0.2)	893 (0.3)	2,123 (0.2)	2,820 (0.2)	650,785 (0.2)
Laterality											
Right (% ^b)	7,132 (11.6)	17,672 (31.5)	30,764 (29.6)	23,849 (31.3)	79,417 (26.7)	2,239 (10.6)	177,934 (31.0)	107,859 (30.0)	288,032 (30.2)	367,449 (29.4)	23,753,144 (7.9)
Left (% ^b)	6,661 (10.9)	14,839 (26.4)	26,698 (25.7)	20,773 (27.2)	68,971 (23.2)	2,556 (12.1)	171,206 (29.8)	111,939 (31.2)	285,701 (29.9)	354,672 (28.3)	20,907,839 (7.0)
Both (% ^b)	5,220 (8.5)	2,023 (3.6)	4,175 (4.0)	2,959 (3.9)	14,377 (4.8)	7,416 (35.2)	31,658 (5.5)	22,517 (6.3)	61,591 (6.5)	75,968 (6.1)	93,568,896 (31.3)
Unspecified (% ^b)	42,228 (69.0)	21,599 (38.5)	42,305 (40.7)	28,687 (37.6)	134,819 (45.3)	8,864 (42.1)	193,082 (33.7)	116,622 (32.5)	318,568 (33.4)	453,387 (36.2)	161,155,400 (53.8)

^aThe proportion of each subtype cases in the selected retinal vascular occlusion population.^bThe proportion of age/gender/laterality group cases in the population of the corresponding diagnosis.

Abbr. IRIS Registry: Intelligent Research in Sight Registry; RAO: Retinal artery occlusion; TRAO: Transient retinal artery occlusion; PRAO: Partial retinal artery occlusion; BRAO: Branch retinal artery occlusion; CRAO: Central retinal artery occlusion; RVO: Retinal vein occlusion; VE: Venous engorgement; BRVO: Branch retinal vein occlusion; CRVO: Central retinal vein occlusion.

Table 2.

Distribution of selected cases of retinal vascular occlusion in analysis cohort by gender and subtype together with estimates of the precision of differences and associations.

	Number of cases	% Men ^a	% Women	% Men – % women	99% CI of % men – % women ^b	OR ^c	99% CI of OR ^c
Retinal vascular occlusion	1,248,656	48.2	51.8	–3.7	(–3.84, –3.51)	0.93	(0.93, 0.93)
RAO	296,887	50.8	49.2	1.6	(1.23, 1.90)	1.03	(1.02, 1.04)
TRAO	61,089	45.1	54.9	–9.8	(–10.54, –9.07)	0.82	(0.80, 0.84)
PRAO	56,027	53.5	46.5	7.0	(6.19, 7.73)	1.15	(1.13, 1.18)
BRAO	103,709	51.3	48.7	2.6	(2.06, 3.19)	1.05	(1.04, 1.07)
CRAO	76,062	52.6	47.4	5.3	(4.61, 5.93)	1.11	(1.09, 1.13)
RVO	951,769	47.3	52.7	–5.3	(–5.50, –5.12)	0.90	(0.89, 0.90)
VE	21,044	44.0	56.0	–12.0	(–13.28, –10.78)	0.79	(0.76, 0.81)
BRVO	572,681	45.5	54.5	–8.9	(–9.16, –8.68)	0.84	(0.83, 0.84)
CRVO	358,044	50.4	49.6	0.9	(0.56, 1.17)	1.02	(1.01, 1.02)

^aH₀ hypothesis states that the proportion of men in each subtype is 50.0%. Two-tailed p<0.0001 for all subtypes using the binomial test.

^bH₀ hypothesis states that the proportions of men and women in each subtype are the same. Two-tailed p<0.0001 for all subtypes using the Z test.

^cThe OR and 99% CI of OR when setting the population of the entire IRIS Registry diagnoses as control with a percentage of men as 50.0%.

Abbr. CI: confidence interval; OR: odds ratio; RAO: Retinal artery occlusion; TRA0: Transient retinal artery occlusion; PRA0: Partial retinal artery occlusion; BRA0: Branch retinal artery occlusion; CRA0: Central retinal artery occlusion; RVO: Retinal vein occlusion; VE: Venous engorgement; BRVO: Branch retinal vein occlusion; CRVO: Central retinal vein occlusion.

Table 3.

Distribution of selected cases of retinal vascular occlusion in analysis cohort by unilateral/bilateral onset and subtype together with estimates of the precision of differences and associations.

	Number of cases with specified laterality	% Unilateral onset ^a	% Bilateral onset	% Unilateral onset – % bilateral onset	99% CI of % unilateral onset – % bilateral onset ^b	OR ^c	99% CI of OR ^c
Entire set of IRIS Registry diagnoses	138,229,879	32.3	67.7	–35.4			
Retinal vascular occlusion	798,089	90.5	9.5	81	(80.84, 81.08)	19.92	(19.77, 20.16)
RAO	162,765	91.2	8.8	82.3	(82.08, 82.59)	21.62	(21.24, 22.22)
TRAO	19,013	72.5	27.5	45.1	(43.91, 46.27)	5.54	(5.30, 5.76)
PRAO	34,534	94.1	5.9	88.3	(87.82, 88.75)	33.67	(31.52, 35.45)
BRAO	61,637	93.2	6.8	86.5	(86.08, 86.82)	28.84	(27.57, 29.94)
CRAO	47,581	93.8	6.2	87.6	(87.16, 87.97)	31.59	(30.19, 33.3)
RVO	635,324	90.3	9.7	80.6	(80.48, 80.75)	19.52	(19.30, 19.73)
VE	12,211	39.3	60.7	–21.5	(–23.08, –19.85)	1.35	(1.29, 1.42)
BRVO	380,798	91.7	8.3	83.4	(83.21, 83.54)	23.11	(22.81, 23.51)
CRVO	242,315	90.7	9.3	81.4	(81.20, 81.63)	20.45	(20.08, 20.81)

^aH₀ hypothesis states that the proportion of unilateral onset cases in each subtype is 32.3% (the proportion of that in the entire set of IRIS Registry diagnoses). Two-tailed p<0.0001 for all subtypes using the binomial test.

^bH₀ hypothesis states that the proportions of unilateral and bilateral onset cases in each subtype are the same. Two-tailed p<0.0001 for all subtypes using the Z test.

^cThe OR and 99% CI of OR when setting the population of the entire IRIS Registry diagnoses as control.

Abbr. CI: confidence interval; OR: odds ratio; RAO: Retinal artery occlusion; TRA0: Transient retinal artery occlusion; PRAO: Partial retinal artery occlusion; BRAO: Branch retinal artery occlusion; CRAO: Central retinal artery occlusion; RVO: Retinal vein occlusion; VE: Venous engorgement; BRVO: Branch retinal vein occlusion; CRVO: Central retinal vein occlusion.

Table 4.

Distribution of selected unilateral cases of retinal vascular occlusion in analysis cohort by right-eye/left-eye onset and subtype together with estimates of the precision of differences and associations.

	Number of unilateral onset cases	% Right-eye ^a	% Left-eye	% Right-eye – % left-eye	99% CI of % right-eye – % left-eye ^b	OR ^c	99% CI of OR ^c
Retinal vascular occlusion	722,121	50.9	49.1	1.8	(1.55, 1.98)	1.04	(1.03, 1.04)
RAO	148,388	53.5	46.5	7	(6.57, 7.51)	1.15	(1.14, 1.17)
TRAO	13,793	51.7	48.3	3.4	(1.86, 4.97)	1.07	(1.02, 1.12)
PRAO	32,511	54.4	45.6	8.7	(7.70, 9.72)	1.19	(1.16, 1.23)
BRAO	57,462	53.5	46.5	7.1	(6.32, 7.84)	1.15	(1.13, 1.18)
CRAO	44,622	53.4	46.6	6.9	(6.03, 7.76)	1.15	(1.12, 1.17)
RVO	573,733	50.2	49.8	0.4	(0.17, 0.65)	1.01	(1.00, 1.01)
VE	4,795	46.7	53.3	–6.6	(–9.26, –3.97)	0.88	(0.81, 0.94)
BRVO	349,140	51.0	49	1.9	(1.62, 2.24)	1.04	(1.03, 1.05)
CRVO	219,798	49.1	50.9	–1.9	(–2.25, –1.47)	0.96	(0.95, 0.98)

^aH₀ hypothesis states that the proportion of right-eye onset cases in each subtype is 50.0%. Two-tailed p<0.0001 for all subtypes except RVO (p<0.01) using binomial test.

^bH₀ hypothesis states that the proportions of right-eye and left-eye onset cases in each subtype are the same. Two-tailed p<0.0001 for all subtypes using Z test.

^cThe OR and 99% CI of OR when setting the population of the entire IRIS Registry diagnoses as control with a percentage of right-eye onset as 50.0%.

Abbr. CI: confidence interval; OR: odds ratio; RAO: Retinal artery occlusion; TRA0: Transient retinal artery occlusion; PRAO: Partial retinal artery occlusion; BRAO: Branch retinal artery occlusion; CRAO: Central retinal artery occlusion; RVO: Retinal vein occlusion; VE: Venous engorgement; BRVO: Branch retinal vein occlusion; CRVO: Central retinal vein occlusion.