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# Risk Factors for Central Retinal Vein Occlusion in Young Adults

A Nationwide Study

Tony Chen, MD, Aditya Uppuluri, MD, Marco Zarbin, MD, PhD, Neelakshi Bhagat, MD, FACS

Institute of Ophthalmology and Visual Science, Rutgers New Jersey Medical School, Newark NJ

# Financial Disclosure

- Dr. Zarbin reports personal fees from Genentech/Roche, personal fees from Novartis Pharma AG, personal fees and other from Iveric bio, personal fees from Ophthotech, other from NVasc, personal fees from Healios KK, personal fees and other from Frequency Therapeutics, personal fees from Chengdu Kanghong Biotech, grants from Aerie Pharmaceuticals, personal fees from Iridex, outside the submitted work.

- No conflicting relationship exists for the other authors.

# Summary

- The most significant risk factors for CRVO in young adults were POAG, retinal vasculitis, and pseudotumor cerebri.
- Hypercoagulable states and DVT/PE also played important roles in the pathogenesis of CRVO in this population.
- Systemic inflammatory conditions were not associated with CRVO; however, retinal vasculitis contributed to CRVO most likely due to its direct inflammatory effect on the vasculature.
- Traditional cardiovascular risk factors such as hypertension and diabetes did not pose significant risk, whereas hyperlipidemia was deemed a significant risk factor.
- Systemic workup for hypercoagulable risk factors are indicated in young CRVO patients, along with treatment of hyperlipidemia.

# Background

- Central retinal vein occlusion (CRVO) is a common retinal vascular disease with potentially vision-threatening complications.
  - Macular edema, neovascularization, vitreous hemorrhage.
- 0.1% to 0.5% of population;[1,2] mostly prevalent in adults > 65 years old.[3]
- Traditional risk factors for CRVO in older adults:[4] age, hypertension, diabetes, hyperlipidemia, and glaucoma.


1. Klein R, Klein BE, Moss SE, et al. The epidemiology of retinal vein occlusion: The beaver dam eye study. *Trans Am Ophthalmol Soc*. 2000;98:133-143.
2. Mitchell P, Smith W, Chang A. Prevalence and associations of retinal vein occlusion in Australia: The blue mountains eye study. *Arch Ophthalmol*. 1996;114(10):1243-1247.
3. Bhagat N, Goldberg MF, Gascon P, Bell W, Haberman J, Zarbin MA. Central Retinal Vein Occlusion: Review of Management. *Eur J Ophthalmol*. 1999;9(3):165-180.
4. Klein R, Moss SE, Meuer SM, Klein BEK. The 15-year cumulative incidence of retinal vein occlusion: The Beaver Dam Eye Study. *Arch Ophthalmol*. 2008;126(4):513-518.

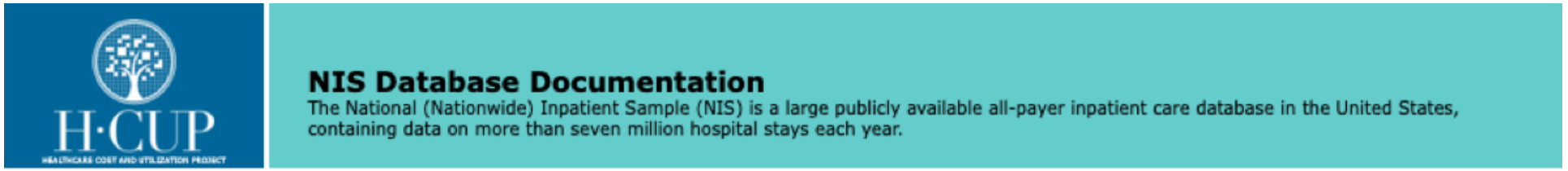
# Study Questions

- 10% -15% of CRVO occurs in patients under the age of 40 years.[5, 6, 7]
- Risk factors of CRVO for young adults are not well-established.
  - Contribution of traditional risk factors?
  - Contribution of hypercoagulability or inflammatory conditions?
  - Do other medical comorbidities in young adults contribute to CRVO?


5. Walters RF, Spalton DJ. Central retinal vein occlusion in people aged 40 years or less: a review of 17 patients. *Br J Ophthalmol*. 1990;74(1):30-35.
6. Bhagat N, Goldberg MF, Gascon P, Bell W, Haberman J, Zarbin MA. Central retinal vein occlusion: Report of two familial cases. *Eur J Ophthalmol*. 1999;9(3):181-195.
7. Hayreh SS, Zimmerman MB, Podhajsky P. Incidence of Various Types of Retinal Vein Occlusion and Their Recurrence and Demographic Characteristics. *Am J Ophthalmol*. 1994;117(4):429-441.

# Data Source

- Patient dataset was obtained from National Inpatient Sample (NIS) database, 2002-2014.
  - Publicly available database managed by the Agency of Healthcare Research and Quality.
  - Included 20% sample of hospitalization in the US; 97% of population.
- Available data includes patient demographics, ICD-9 diagnosis codes, length and cost of stay, and associated medical comorbidities, etc.



# Study Method

Study group: Patients age 18 – 40 with primary admitting diagnosis of CRVO, identified using ICD-9 code 362.35

Control group: Age- and gender-matched non-CRVO patients, generated and randomly selected from NIS using IBM SPSS 23 (43:1 weighted control-case ratio).

Statistical analyses of selected comorbidities (chi-square, Firth univariate and multivariate logistic regression analyses). $P<0.05$ was considered statistically significant.

# Risk Factor Selection

- Aortic Dissection/Aneurysm
- Arterial Thromboembolic Disease + Coronary Artery Disease
- Bleeding Diathesis
- Congestive Heart Failure
- DVT and PE (History)
- Diabetes Mellitus
- Drug Use (IV)
- Drug Use (non-IV)
- Hyperlipidemia
- Hypercoagulable State
- Hypertension
- Lyme Disease
- Migraine
- Obesity
- Peripheral Vascular Disease
- Pregnancy
- Pseudotumor Cerebri
- Rheumatoid Arthritis/Collagen Vascular Disease
- Sickle Cell Trait and Disease
- Tobacco Use
- Stroke (History) – ischemic and non-ischemic
- Syphilis
- Systemic Vasculitides

**Ocular Conditions:**

- POAG
- Retinal Vasculitis

**Excluded (N=0 in both study and control groups):**

- Atherosclerosis (systemic except carotid and coronary)
- Cocaine Use
- Oral Contraceptive Use
- Open-Globe Injury
- Non-Stroke Cerebrovascular Disease

# Patient Demographics

| | Central Retinal Vein Occlusion | | | | |
|---|---|---|---|---|---|
| | **No (Weighted N = 4076)** | | **Yes (Weighted N = 95)** | | |
| | Count | Column N % | Count | Column N % | P Value |
| ***Sex*** | | | | | 0.924 |
| **Men** | 1779 | 43.6% | 41 | 42.9% | |
| **Women** | 2297 | 56.4% | 54 | 57.1% | |
| **Average Age (years)** | 30.9±6.3 | - | 31.4±6.4 | - | 0.403 |
| ***Age (years)*** | | | | | 0.270 |
| **18-24** | 850 | 20.8% | 15 | 15.6% | |
| **25-32** | 1218 | 29.9% | 45 | 36.3% | |
| **33-40** | 2008 | 49.3% | 46 | 48.1% | |

# Chi-Square Analysis

| | Central Retinal Vein Occlusion | | | | |
|---|---|---|---|---|---|
| | No (Weighted N = 407) | | Yes (Weighted N = 95) | | |
| | Count | Column N % | Count | Column N % | P Value |
| **Hypertension** | 413 | 10.2% | 15 | 15.4% | 0.076 |
| **Diabetes Mellitus** | 198 | 4.9% | 10 | 10.5% | 0.013 |
| **Hyperlipidemia** | 115 | 2.8% | 10 | 10.4% | < 0.001 |
| **Obesity** | 208 | 5.1% | 5 | 5.3% | 0.954 |
| **POAG** | 0 | 0.0% | 6 | 6.0% | < 0.001 |
| **Hypercoagulable State** | 10 | 0.2% | 10 | 10.5% | < 0.001 |
| **DVT/PE (History)** | 34 | 0.8% | 16 | 16.5% | < 0.001 |
| **Pseudotumor Cerebri** | 5 | 0.1% | 5 | 5.3% | < 0.001 |
| **Retinal Vasculitis** | 0 | 0.0% | 5 | 4.9% | < 0.001 |

# Logistic Regression Analysis

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| **Comorbidities** | **OR (95% CI)** | **P Value** | **OR (95% CI)** | **P Value** |
| **Hypertension** | 1.64 (0.94 - 2.88) | 0.081 | - | - |
| **Diabetes Mellitus** | 2.39 (1.24 – 4.61) | 0.010 | 1.21 (0.46 – 3.12) | 0.694 |
| **Hyperlipidemia** | 4.18 (2.13 - 8.18) | < 0.001 | 3.60 (1.57 – 8.30) | 0.003 |
| **POAG** | 558.86 (24.35 - 12824.38) | < 0.001 | 836.72 (36.28 – 19295.13) | < 0.001 |

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| **Comorbidities** | **OR (95% CI)** | **P Value** | **OR (95% CI)** | **P Value** |
| **Hypercoagulable State** | 47.54 (19.28 - 117.19) | < 0.001 | 25.25 (7.78 – 81.97) | < 0.001 |
| **DVT/PE (History)** | 23.74 (12.57 – 44.83) | < 0.001 | 21.88 (10.58 – 45.26) | < 0.001 |
| **Pseudotumor Cerebri** | 45.28 (12.85 - 159.52) | < 0.001 | 35.94 (9.19 – 142.99) | < 0.001 |
| **Rheumatoid Arthritis and Collagen Vascular Disease** | 9.98 (3.84 - 25.97) | < 0.001 | 0.91 (0.06 – 14.47) | 0.949 |
| **Systemic Vasculitides** | 3.87 (0.16 - 92.94) | 0.404 | - | - |
| **Retinal Vasculitis** | 466.43 (18.96 - 11474.48) | < 0.001 | 705.82 (28.55 – 17448.63) | < 0.001 |

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| **Comorbidities** | **OR (95% CI)** | **P Value** | **OR (95% CI)** | **P Value** |
| **Sickle Cell Trait and Disease** | 0.31 (0.02 - 5.13) | 0.413 | - | - |
| **Bleeding Diathesis** | 0.23 (0.01 - 3.76) | 0.301 | - | - |
| **Migraine** | 8.95 (4.45 – 18.00) | < 0.001 | 2.53 (0.86 – 7.49) | 0.092 |
| **Aortic Dissection/Aneurysm** | 2.36 (0.12 - 48.11) | 0.578 | - | - |
| **Arterial Thromboembolic Disease + Coronary Artery Disease** | 0.37 (0.02 - 6.12) | 0.484 | - | - |
| **Congestive Heart Failure** | 1.01 (0.06 - 18.04) | 0.993 | - | - |
| **Peripheral Vascular Disease** | 2.06 (0.10 - 40.91) | 0.635 | - | - |
| **Stroke (History) – ischemic and non-ischemic** | 2.21 (0.11 – 44.56) | 0.603 | - | - |

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| **Comorbidities** | **OR (95% CI)** | **P Value** | **OR (95% CI)** | **P Value** |
| **Drug Use (IV)** | 0.58 (0.03 - 9.83) | 0.704 | - | - |
| **Drug Use (non-IV)** | 0.06 (0.00 - 0.95) | 0.046 | 0.10 (0.01 – 1.65) | 0.108 |
| **Tobacco Use** | 0.87 (0.50 – 1.49) | 0.601 | - | - |
| **Obesity** | 1.12 (0.47 - 2.69) | 0.797 | - | - |
| **Pregnancy** | 0.82 (0.05 - 14.31) | 0.891 | - | - |
| **Syphilis** | 3.57 (0.15 - 82.83) | 0.428 | - | - |
| **Lyme Disease** | 3.87 (0.16 - 92.94) | 0.404 | - | - |

# Summary

- The most significant risk factors for CRVO in young adults were POAG, retinal vasculitis, and pseudotumor cerebri.
- Hypercoagulable states and DVT/PE also played important roles in the pathogenesis of CRVO in this population.
- Systemic inflammatory conditions were not associated with CRVO.
- Traditional cardiovascular risk factors such as hypertension and diabetes did not pose significant risk, whereas hyperlipidemia was deemed a significant risk factor.
- Systemic workup for hypercoagulable risk factors are indicated in young CRVO patients, along with treatment of hyperlipidemia.

# Limitations

- Validity of the study results depends on accuracy and specificity of ICD-9 codes in the NIS database.
- ICD-9 diagnosis code is not as specific as ICD-10. Specific diagnosis codes were not available for certain diseases.
- This study only included patients who were hospitalized with a primary admitting diagnosis of CRVO. Patients with CRVO are not usually admitted to the hospital for treatment unless in the presence of severe comorbid condition that requires management. May not be applicable to a different patient population.

# References


1. Klein R, Klein BE, Moss SE, et al. The epidemiology of retinal vein occlusion: The beaver dam eye study. *Trans Am Ophthalmol Soc*. 2000;98:133-143.

2. Mitchell P, Smith W, Chang A. Prevalence and associations of retinal vein occlusion in Australia: The blue mountains eye study. *Arch Ophthalmol*. 1996;114(10):1243-1247.

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