Journal of
Ophthalmology: Open Access

Research Article Open Access

Increased Risk of Central Retinal Vein Occlusion in Patients with Inflammatory Bowel Disease: A Population-Based Study

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Received Date: November 09, 2022 **Accepted Date:** December 09, 2022 **Published Date:** December 12, 2022

Citation: Antoine Boustany, Marc Mardelli, Somtochukwu Onwuzo, Alyssa Coleman, Hadi Khaled Abou Zeid, Ashraf Almomani, Imad Asaad (2022) Increased Risk of Central Retinal Vein Occlusion in Patients with Inflammatory Bowel Disease: A Population-Based Study. J Ophthalmol Open Access 6: 1-9.

Abstract

Introduction: Central retinal vein occlusion (CRVO) is a retinal vascular disorder resulting from thrombus formation in the retrolaminar portion of the intraretinal venous tree. It is well known that conditions contributing to the development of cardiovascular and peripheral vascular disease, such as hypertension and diabetes, are also risk factors for the development of this vascular pathology. To a lesser degree, it has been suggested in available case series and case reports that inflammatory bowel disease (IBD) may also predispose individuals to CRVO formation. Until now, no studies have been conducted to demonstrate a statistically significant association between these two entities. Therefore, the aim of our study is to assess whether patients with IBD, specifically Crohn's disease and ulcerative colitis, are at a greater risk for CRVO development than individuals without this comorbidity.

Methods: Explorys Inc., Cleveland, OH, USA is a validated multicenter research platform database involving more than 360 hospitals and 26 healthcare systems across the United States and consisting of data accumulated from 9/1999- 9/2022. Adults from 18 to 65 years of age were included in the study. Patients with a history of glaucoma, pregnancy, and autoimmune diseases (not including IBD) were excluded. A multivariate regression analysis was performed to account for potential confounders including a history of ulcerative colitis, Crohn's disease, hyperlipidemia, type 2 diabetes mellitus, smoking, OCP use, and hypertension. A two-sided P value <0.05 was considered statistically significant, and all statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria, 2008).

Results: 80,685,740 individuals aged 18 to 65 years were screened in the database and 48,015,670 were selected. 45,858,310 were included after excluding for pregnancy, glaucoma, and autoimmune diseases (not including IBD). The 20-year-period

prevalence rate of Crohn's disease and ulcerative colitis was the highest among patients aged 35-40 and 60-65 (Figure 1). To adjust for confounding variables, a multivariate regression analysis was performed (Table 1). In a first analysis where we controlled for Crohn's disease, risk of CRVO was greater in patients with hyperlipidemia (OR: 4.66; 95% CI: 4.25-5.11), hypertension (OR: 2.41; 95% CI: 2.16-2.69), type 2 diabetes mellitus (OR: 2.69; 95% CI: 2.44-2.96), Crohn's disease (OR: 4.85; 95% CI: 3.71-6.21), smoking history (OR: 1.49; 95% CI: 1.34-1.66), and OCP users (OR: 1.63; 95% CI: 1.31-1.99). In a second analysis where we controlled for ulcerative colitis, risk of CRVO was increased in patients with hyperlipidemia (OR: 4.51; 95% CI: 4.11-4.93), hypertension (OR: 2.37; 95% CI: 2.12-2.63), type 2 diabetes mellitus (OR: 2.63; 95% CI: 2.38-2.90), ulcerative colitis (OR: 4.50; 95% CI: 3.36-5.90), smoking history (OR: 1.47; 95% CI: 1.32-1.64), and OCP users (OR: 1.50; 95% CI: 1.20-1.85).

Conclusions: Our study illustrates a significantly increased risk of central retinal vein occlusion in patients with Crohn's disease or ulcerative colitis, independent of identified confounding variables. Younger patients suffering from CRVO frequently undergo an extensive hypercoagulable workup without elucidation of an underlying etiology. Therefore, it is important to consider IBD in the differential diagnosis of CRVO in younger individuals. Further studies are needed to understand the exact mechanism in which IBD increases the risk of developing CRVO.

Keywords: Inflammatory Bowel Disease; Ulcerative Colitis; Crohn's Disease; Central Retinal Vein Occlusion.

Abbreviations: CD, Crohn's disease; CI, confidence interval; CRVO, central retinal vein occlusion; EHR, electronic health record; EIM, extra intestinal manifestation; IBD, inflammatory bowel disease; IRB, institutional review board; OCP, oral contraceptive pills; OR, odd ratio; SNOMED-CT, Systematized Nomenclature of Medicine-Clinical Terms; UC, ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) refers to a category of chronic inflammatory conditions affecting the gastrointestinal tract [1].The two main entities include Crohn's disease (CD) and ulcerative colitis (UC) [1].IBD affects a large population with a prevalence of more than 1.5 and 2 million individuals in North America and Europe respectively [2].Among those diagnosed with IBD, 25% present prior to the age of 20 [1].The presenting signs and symptoms of IBD are varied, but may be broadly categorized as being either intestinal (e.g., abdominal pain, diarrhea, rectal bleeding, oral ulcers, constipation) or extraintestinal (e.g., erythema nodosum, arthritis, osteoporosis, growth failure, episcleritis, uveitis, iritis, pancreatitis, anemia)[1].The myriad of ways in which a patient with CD or UC may initially present has the capacity to delay appropriate diagnosis and initiation of treatment.

Central retinal vein occlusion (CRVO) is a vision-threatening retinal vascular disorder resulting from thrombus formation in the retrolaminar portion of the intraretinal venous tree [3-5]. Prognosis of visual potential following this insult is partially dependent on disease sequelae such as macular edema, vitreous hemorrhage, neovascularization, and neovascular glaucoma [4]. Established risk factors for CRVO consist of entities that promote clot formation via mechanisms described in Virchow's triad. These risk factors are categorized as being either that of a systemic process or localized to the eye. Systemic risk factors include diseases such as hypertension, diabetes mellitus, hyperlipidemia, systemic vasculitis, hematologic neoplasia, protein S deficiency, and antiphospholipid syndrome. Ocular risk factors include glaucoma, decreased ocular perfusion pressure, and orbital neoplasms [5]. The greatest prevalence of CRVO is observed in the older adult population at a rate of 0.75% in those aged 80-89 years old whereas younger individuals from age 30-39 have a prevalence of only 0.03% [3]. Younger healthy patients that present with CRVO undergo an extensive workup to identify underlying factors that may be contributing to a hypercoagulable state. Unfortunately, in many instances, the etiology of disease in such patients remains unknown.

To our knowledge, despite multiple case reports and case series suggesting the presence of a positive correlation between IBD and development of CRVO, there has yet to be a nationwide study that quantifies the relationship between these two entities [6-9].Therefore, the aim of this study is to procure such quantification by conducting a large-scale multi-center population-based retrospective study to assess whether there is a statistically significant increased risk of CRVO in individuals with IBD.

Methods

Database

Explorys Inc., Cleveland, OH, USA is a validated multicenter and research platform database of more than 360 hospitals from 26 different healthcare systems across the United States consisting of data accumulated from 1999 to September 2022. Explorys was developed and has been prospectively maintained by IBM Corporation, Watson Health [10], including electronic health record (EHR) from greater than 60 million unique patients and provide a broad regional distribution of the United States representing approximately 15% of the population. It was utilized to construct a retrospective cohort analysis. A Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) hierarchy [11] was used to select diagnoses, findings, and procedures. Prescription drug orders are mapped into SNOMED and RxNorm [12]. Institutional Review Board (IRB) was not required as source data are de-identified. To protect patient confidentiality, Explorys rounds population counts to the nearest 10 and treats all counts between zero and 10 as equivalent. The study was conducted in accordance to the Declaration of Helsinki (as revised in 2013). Access to the database is granted to participating healthcare systems. Use of the Explorys platform has been validated in multiple fields including gastroenterology [13,14].

Patient selection

Adults from 18 to 65 years of age were included in the study. Patients with a history of glaucoma, pregnancy, and autoimmune diseases (not including IBD) were excluded. A subgroup of patients with a diagnosis of "central retinal vein occlusion" (CRVO) was later selected and used in the analysis. The control group was identified as adult patients who did not have a diagnosis of CRVO.

Statistical analysis

Patients who developed CRVO were compared to those who did not. The prevalence rate of IBD, Crohn's disease, and ulcerative colitis was calculated and compared among different age groups. It was also calculated in the general US population. The annual incidence of IBD was also calculated. The risk of CRVO in the cohort was calculated using a univariate regression. A multivariate regression analysis was performed to account for potential cofounders including a history of ulcerative colitis, Crohn's disease, hyperlipidemia, type 2 diabetes mellitus, smoking, OCP use, and hypertension. A two-sided P value <0.05 was considered as statistically significant, and all statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria, 2008).

Results

Descriptive epidemiology

80,685,740 individuals aged 18 to 65 years were screened in the database and 48,015,670 were selected. 45,858,310 were included after excluding pregnancy, glaucoma, and autoimmune diseases. The baseline characteristics of our cohort are displayed in Table 1. The 20-year-period prevalence rate of IBD, Crohn's disease, and ulcerative colitis was the highest among patients aged 35-40 and 60-65 (Figure 1). The total prevalence of Crohn disease and ulcerative colitis was 310 and 260 per 100,000 individuals respectively. The annual incidence of Crohn disease and ulcerative colitis was 150 and 111 per 100,000 individuals respectively.

Caucasian (61.70%) and African American (19.56%) race was more common in patients with CRVO compared to the one without the disease. Type 2 diabetes mellitus (31.13%), benign hypertension (19.28%), hyperlipidemia (48.58%), obesity (28.09%), IBD (1.92%), Crohn's disease (1.37%), ulcerative colitis (1.10%), smoking (14.05%), cannabis use (1.65%), and OCP (1.93%) were higher in the case group category as well.

Table 1: Baseline characteristics of patients with CRVO and control

		CRVO (%)	No CRVO (%)
	Total	n= 3,630	n= 46,039,770
Race	Caucasian	2,240 (61.70)	23,381,500 (50.78)
	African American	710 (19.56)	5,089,560 (11.05)
	Asian	60 (1.65)	751,630 (1.63)
Comorbidities	Type 2 Diabetes Mellitus	1,130 (31.13)	2,051,600 (4.45)
	Benign Hypertension	700 (19.28)	1,054,150 (2.29)
	Hyperlipidemia	1,800 (48.58)	4,326,260 (9.39)
	Obesity	1,020 (28.09)	3,086,940 (6.70)
	IBD	70 (1.92)	181,110 (0.39)
	Crohn's disease	50 (1.37)	144,050 (0.31)
	Ulcerative colitis	40 (1.10)	105,710 (0.22)
	Hypothyroidism	380 (10.47)	1,421,850 (7.90)
Substance abuse	Smoking	510 (14.05)	2,554,870 (3.08)
	Cannabis	60 (1.65)	441,270 (0.96)
Medications	OCP	70 (1.93)	850,630 (1.84)

Abbreviations: CRVO, central retinal vein occlusion; IBD, inflammatory bowel disease; OCP, oral contraceptive pills

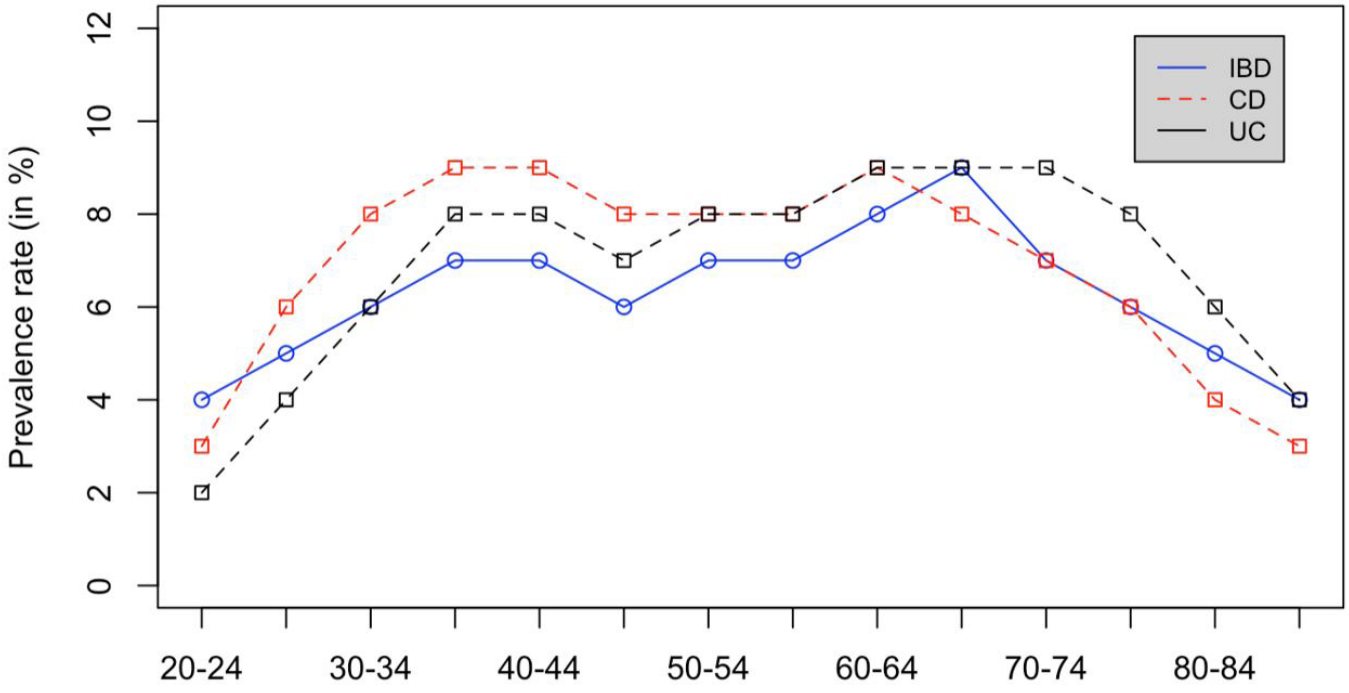

Figure 1: Prevalence rate of IBD, Crohn's disease, and ulcerative colitis among different age groups

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis

Risk and predictors of CRVO in patients using a univariate regression analysis

The risk of being diagnosed with CRVO was increased in patients with hyperlipidemia (OR: 8.58; 95% CI: 7.97-9.24), type 2 diabetes mellitus (OR: 8.40; 95% CI: 7.73-9.12), hypertension (OR: 9.43; 95% CI: 8.55-10.38), Crohn's disease (OR: 7.01; 95% CI: 5.37-8.96), ulcerative colitis (OR: 7.55; 95% CI: 5.63-9.86), smoking history (OR: 2.83; 95% CI: 2.54-3.14), and OCP users (OR: 1.75; 95% CI: 1.41-2.15) as reported in Table 2.

Risk and predictors of CRVO in patients using a multivariate regression analysis

In order to adjust for confounding variables, a multivariate regression analysis was performed (Table 3).

In a first analysis where we controlled for Crohn's disease, risk of CRVO was increased in patients with hyperlipidemia (OR: 4.66; 95% CI: 4.25-5.11), hypertension (OR: 2.41; 95% CI: 2.16-2.69), type 2 diabetes mellitus (OR: 2.69; 95% CI: 2.44-2.96), Crohn's disease (OR: 4.85; 95% CI: 3.71-6.21), smoking history (OR: 1.49; 95% CI: 1.34-1.66), and OCP users (OR: 1.63; 95% CI: 1.31-1.99).

In a second analysis where we controlled for ulcerative colitis, risk of CRVO was increased in patients with hyperlipidemia (OR: 4.51; 95% CI: 4.11-4.93), hypertension (OR: 2.37; 95% CI: 2.12-2.63), type 2 diabetes mellitus (OR: 2.63; 95% CI: 2.38-2.90), ulcerative colitis (OR: 4.50; 95% CI: 3.36-5.90), smoking history (OR: 1.47; 95% CI: 1.32-1.64), and OCP users (OR: 1.50; 95% CI: 1.20-1.85).

Table 2: Risk of developing CRVO using univariate regression analysis model

CRVO		
	OR (95% CI)	**P-value**
Hyperlipidemia	8.58 (7.97-9.24)	<0.001
Type 2 diabetes mellitus	8.40 (7.73-9.12)	<0.001
Crohn's disease	7.01 (5.37-8.96)	<0.001
Ulcerative colitis	7.55 (5.63-9.86)	<0.001
Smoking	2.83 (2.54-3.14)	<0.001
OCP	1.75 (1.41-2.15)	<0.001
Hypertension	9.43 (8.55-10.38)	<0.001

Abbreviations: CI, confidence interval; OCP, oral contraceptive pills; OR, odd ratio

Table 3: Risk of developing CRVO using multivariate regression analysis model

	CRVO				
	OR (95% CI)	**P-value**		**OR (95% CI)**	**P-value**
Hyperlipidemia	4.66 (4.25-5.11)	<0.001	**Hyperlipidemia**	4.51 (4.11-4.93)	<0.001
Type 2 diabetes mellitus	2.69 (2.44-2.96)	<0.001	**Type 2 diabetes mellitus**	2.63 (2.38-2.90)	<0.001
Crohn's disease	4.85 (3.71-6.21)	<0.001	**Ulcerative colitis**	4.50 (3.36-5.90)	<0.001
Smoking	1.49 (1.34-1.66)	<0.001	**Smoking**	1.47 (1.32-1.64)	<0.001
OCP	1.63 (1.31-1.99)	<0.001	**OCP**	1.50 (1.20-1.85)	<0.001
Hypertension	2.41 (2.16-2.69)	<0.001	**Hypertension**	2.37 (2.12-2.63)	<0.001

Abbreviations: CI, confidence interval; OCP, oral contraceptive pills; OR, odd ratio

Discussion

Based on the analysis conducted, we found that patients diagnosed with Crohn's disease and ulcerative colitis are at 4.85- and 4.50-fold higher risk of developing a CRVO respectively. Our data also demonstrates that hyperlipidemia, type-2 diabetes mellitus, hypertension, smoking, and OCP use are risk factors for the development of CRVO. It was interesting to note that these factors showed similar results after controlling for CD and UC, which aligns with previously published articles [15].

IBD, considered an emerging global disease, is a systemic inflammatory disorder primarily impacting the gastrointestinal system with sequelae affecting other organ systems as well. Prior publications have reported an exponential increase in disease incidence over the past several decades, particularly in westernized countries [16-18]. A systematic review conducted in 2012 involving studies gathered from 1920 to 2004, showed an annual incidence rate in North America as high as 19.2 per 100,000 for UC and 20.2 per 100,000 for CD. Disease prevalence reached 248.6 per 100,000 for UC and 318.5 per 100,000 for CD, which is comparable to our findings with an annual incidence rate of 0.011% for UC and 0.015% for CD and a prevalence of 0.26% for UC and 0.31% for CD [18]. Additionally, we noted the greatest number of individuals impacted were in their 3rd and 6th decade of life (Figure 1). The difference seen in both studies demonstrates the ongoing increase in IBD incidence, not only in westernized societies but also in developing countries [18]. This debilitating group of diseases have peak incidences affecting patients early on in their life (20-29 years of age), resulting in long term cost to the patient and a burden to the healthcare system, increasing morbidity and mortality [18]. Extraintestinal manifestations (EIM) are a group of IBD-associated symptoms involving organs other than those of the gastrointestinal system. An interplay between various immune mechanisms can explain the pathogenesis of EIM [19]. Indeed, it was noted that molecular mimicry based on the similarity between microbiota and affected tissue antigens could be one of the causes of the autoimmune reaction against self-organs in IBD [19,20]. In addition, several cytokines like TNF-alpha which are overexpressed in IBD can cause damage to tissues[19,20]. It has also been speculated that EIM can result from the invasion of extraintestinal organs by gut-lymphocytes expressing tissue-specific chemokines or integrins [19,20]. On the other hand, smoking has been documented to play a role in EIM [19,20]. A genetic component has also been linked to the development of EIM, such as several human leukocyte antigens (HLA) genotype variations that carry an increased risk of EIM in CD, such as HLA-A2, HLA-DR1 and HLA-DQw5 and UC, such as HLA-DR103, HLA-B58, and HLA-B27 [19]. EIM are common with up to 47% of patients experiencing at least one EIM during the course of their disease. 25.8% of patients present with at least one EIM. When the EIM experienced is uveitis, 52.2% of cases present with this ophthalmic manifestation prior to being diagnosed with an IBD[19]. Additional ophthalmic EIMs frequently observed include episcleritis, scleritis, and conjunctivitis. Less common ophthalmic EIMs have also been reported and include retinitis, central retinal artery occlusion, and retinal vasculitis which can lead to marked loss of vision [20]. CRVO has been described in several case report and case series as an EIM with devastating visual outcomes [6,7,8,9,22,23,24].

While the exact pathogenesis of CRVO is not well understood, one established hypothesis suggests that arteriosclerotic changes within the central retinal artery posterior to the lamina cribrosa exert compression upon the central retinal vein [25,26]. This follows the principle of Virchow's triad for thrombogenesis where compression causes endothelial damage, venous stasis, and localized hypercoagulability within the central retinal vein. An alternative hypothesis proposes CRVO to be the ophthalmic manifestation of systemic vasculitis seen in those with IBD. Retinal vasculitis has been reported in CD, which has a markedly occlusive effect on the central retinal vein leading to a non-ischemic type [25]. IBD is believed to create a prothrombic state, but the underlying pathophysiology remains to be identified. Mechanisms previously suggested include hyperfibrinogenemia, protein C and S deficiency, antithrombin III deficiency, decreased tissue-type plasminogen activator activity, prolonged thrombin and prothrombin time, and high plasminogen activator inhibitor levels [22-27]. It usually presents in the more elderly population but in patients with IBD, CRVO are seen more commonly in younger patients. A recent population-based study conducted by Grainge et al. compared VTE rates between IBD and non-IBD patients. This study found a 3.4-fold higher risk of VTE and an overall VTE incidence of 0.26% per year in IBD patients [28]. The hypercoagulable state present in patients with IBD results in greater susceptibility to CRVO development, as demonstrated by our study findings when controlling for confounding variables. Other risk factors, such as hyperlipidemia and hypertension, that have been very well established causes of atherosclerosis have been also linked to increase the risk of developing a retinal vein occlusion. In a meta-analysis conducted by O'Mahoney et al., it was observed that patients diagnosed with hyperlipidemia and systemic hypertension are at 3.5 and 2.5 times higher risk of developing any form of retinal vein occlusion

[29]. Moreover, Chen et al. found a 3-times increase in the risk of CRVO in young patients with hyperlipidemia. Interestingly, they did not find a significant relationship between CRVO and hypertension and diabetes mellitus in this population [15]. Several articles in the literature have attributed the increased propensity for CRVO in the setting of hyperlipidemia to platelet activation caused by abnormal lipid profiles [15,30]. In fact, Dodson et al, described elevated levels of beta-thromboglobulin, a platelet factor, in patients with dyslipidemia suggesting increased platelet activation. Subsequently, platelets would aggregate and precipitate a pre-thrombotic state, a major factor in the pathogenesis of CRVO [30]. On the other hand, elevated Total Cholesterol and LDL were correlated with an increase in serum viscosity and were predictive of the severity of RVO [31].

Some limitations of this study include the characteristics inherent to the database used. We were unable to verify patient information since all protected health information was de-identified, leaving findings vulnerable to misclassification or misrepresentation of a diagnosis. Additionally, the lack of information regarding how the disease was diagnosed, imaging used, laboratory results, pathology reports, patient's age, number of medications taken further limited the study. Furthermore, there was no access to the patient's clinical data to confirm whether the diagnostic criteria of CRVO, IBD, UC, and CD were respected. Factors that strengthen the reliability of this study include the large sample size comprised of a wide range of ages and ethnicities, the extensive period of time over which data was collected, and the ability to control for confounding variables. The substantial sample size also enhances the generalizability of our study findings to other populations.

Conclusion

In conclusion, there is a statistically significant increased risk of developing CRVO for individuals with IBD, either CD or UC, compared to those without IBD. Given the potentially devastating consequences of CRVO, including markedly reduced visual acuity, it is important educate individuals with IBD on the possibility of disease development. As there is no known effective medical treatment available for the prevention or treatment of CRVO at this time, it is essential that subsequent complications such as macular edema and neovascularization be properly managed to avoid further reduction in visual acuity. It is possible that decreased frequency of flares and greater optimization of IBD management may lessen the risk of CRVO development. Furthermore, certain IBD treatments, including biologics, may be more adept at dampening thrombogenesis than others. Additional research is needed to assess the above so as to elucidate strategies with which the incidence of this devastating retinal vascular disease may be reduced in the IBD population.

Financial support

None declared

Conflict of interest

None declared

Consent

Not needed

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