Prognostic Factors for Recurrence of Macula Edema in Central Retinal Vein Occlusions after Intravitreal Anti-VEGF Injections: A Comparative Study

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Abstract

Purpose: To examine the prognostic factors for recurrence of macula edema in central retinal vein occlusions (CRVO) after anti-vascular endothelial growth factor treatment (anti-VEGF).

Methods: A retrospective study of 116 patients with CRVO treated with at least 3 intravitreal injections of anti-VEGF at a tertiary care hospital. Age, gender, fasting blood sugar, blood pressure, visual acuity, fundus image and OCT macula was collected for each patient. The data was descriptively and comparatively analyzed using Chi-square test, independent t-test and Mann-Whitney U-test.

Results: Of the 116 patients enrolled, 2 groups of 58 patients had recurrent and non-recurrent macula edema after treatment with at least 3 intravitreal anti-VEGF injections for CRVO respectively. The mean age was 59.94 ± 12.50 for both groups, hyper-reflective foci was more common in the recurrent group 44.8% vs 22.4% (P = 0.011), Triglycerides (115.12 ± 33.73 vs 94.25 ± 29.99, P = 0.011) and HbA1c (7.38 ± 1.02 vs 6.64 ± 1.36, P = 0.007) were found to be higher in the recurrent group. Central subfield thickness was found to be thicker in the recurrent group (460.60 ± 76.51 vs 445.60 ± 111.30, P = 0.073).

Conclusion: Patients with CRVO and recurrent macula edema are associated with hyper-reflective foci, higher levels of triglycerides and HbA1c. These findings can be helpful in prognosticating recurrence of macula edema in these patients.

Keywords: Central retinal vein occlusion, Recurrence macula edema, Central subfield thickness, Hyper reflective foci

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Introduction

The pathology of the disease entity known as retinal vein occlusion (RVO) is due to the hardening and thickening of the walls of the retinal veins resulting in occlusion within the lumen.[1-4] The presentation of central retinal vein occlusions (CRVO) consists of dilated and tortuous venous vessels, retinal hemorrhages, flame shaped hemorrhages and at times, optic disc edema. Whereas the hemiretinal vein occlusions are defined by dilated and tortuous venous vessels, retinal hemorrhages, flame shaped hemorrhages in the upper half or lower half of the vascular arcade. Furthermore, macula edema can be present in either central or branch retinal vein occlusions.[5] The pathology of the retinal vein occlusions are affected by various factors such as increasing age and presence of diabetes, hypertension and hyperlipidemia.[6,7]

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Various studies suggest increasing age and hypertension are two significant factors contributing to retinal vein occlusions.[4,8,9] Furthermore, 30% of patients with retinal vein occlusions have coexisting diabetes and hypertension.[7,10] While 54% and 8% of patients with vein occlusions have either hypertension or diabetes respectively.[11]

The cause of decreased vision in patients with retinal vein occlusion is of macula edema. In the past, treatment of the resulting macula edema with grid laser treatment did not result in significant improvements in patient vision.[12] Currently, using intravitreal anti-vascular endothelial growth factor (VEGF) treatment is effective in reducing macula edema in retinal vein occlusions and improving patient vision.[13-15] Evidence also suggests the treatment can result in prolonged maintenance of this improved vision, however, a group of patients experience recurrence of macula edema.[16,17] The recurrence is thought to be due to a number of factors, literature suggests patients with hypertension, in addition to patients with ischemic type RVO carry a highest risk of recurrence.[17]

This study focuses on patients with retinal vein occlusions with macula edema to investigate the cause and associations with disease morphology and demographic characteristics. The data from this study provides insight into treatment, prevention and prognostication of the recurrence in macula edema and its effects on visual acuity of patients with retinal vein occlusion.

Methods

Data was collected retrospectively in patients with retinal vein occlusion at the vitreo-retinal clinic at Thammasat University Hospital between January 2012 and December 2022. This study was approved by the ethics committee for human research at Thammasat University.

The inclusion criteria for patients in this study are those diagnosed with retinal vein occlusion (including hemi and central retinal vein occlusions, as we deem them to have similar pathologies) aged 18 or above who have received a completed treatment course of at least three intravitreal anti-VEGF injections, followed by further *pro re nata* injections decided by the treating retina specialist. The exclusion criteria for patients in this study are those with a history of vitreoretinal surgery or other ocular surgery prior to the study, incomplete clinical records, follow up duration of less than 1 year or those diagnosed with other causes of macula edema.

The clinical data collected consisted of the type of retinal vein occlusion (hemi and central vein occlusions), age, gender, smoking, alcohol intake, baseline best corrected visual acuity (BCVA), central subfield thickness (CST), presence of diabetes mellitus, HbA1c, dyslipidemia, hypertension, type and dosage of anti-VEGF treatment received (Bevacizumab 1.25 mg, Ranibizumab 0.5 mg, or Aflibercept 2 mg). In this study, the number of intravitreal anti-VEGF injections corresponds to the amount required to achieve no further leakage in the macula and improvement of at two lines on the Snellen visual acuity chart. The visual acuity was recorded using the Snellen chart which was subsequently converted to the approximate ETDRS letter equivalent using an equation (approximate ETDRS letter score = 85+50 x log Snellen fraction).[23]

All patients in this study had optical coherence tomography images of their macula taken (Cirrus HD-OCT5000™; Carl Zeiss, Dublin, California, USA). From the first to their last follow up, the morphology and central subfield thickness have been followed up for at least 1 year. The definition for recurrence of macula edema is the deterioration of visual acuity of at least 5 ETDRS letters and at least a 10% increase of central subfield thickness, in addition to increased intraretinal or subretinal fluid after cessation of intravitreal anti-VEGF therapy for at least 2 months.[17] No Fluorescein Angiogram imaging was used in this study as it was a retrospective study in a clinical setting where FA was not part of a routine follow up.

Statistical analysis

Statistical analysis has been made using SPSS version 23.0.

1. Numerical collected data are presented using descriptive statistics in mean, standard deviation, median and range.

2. Analytical statistics are presented with a P value of <0.05 considered as being significant.

2.1 Categorical data such as gender, age, smoking and type of RVO were comparatively analyzed using Chi-square test, and in those variables with expected cell <5 in more than 25%, Fisher's Exact test was used.

2.2 comparison of means with continuous variable data between the recurrent and non-recurrent group such as age, CST of macula, intraocular pressure and number of injections-independent T-Test.

Results

Of the 116 patients included in this study, the majority of the patients in both the recurrent and non-recurrent group have a mean age of 59.94 ± 12.50, males are more common than females (66 and 50 respectively). Hypertension, diabetes mellitus and history of smoking is present in 78.4%, 70.7% and 46.6% of these patients respectively. The average central subfield thickness of these patients is 460.60 ± 76.51 and 445.60 ± 111.30 in the recurrent and non-recurrent group respectively. Furthermore, hyper reflective retinal foci in the recurrent and non-recurrent group (44.8% and 22.4% P value <0.011) are significantly different. (table1)

Table 1: Baseline characteristics and Clinical Variables of patients between *recurrence group* and *non-recurrence group* (n=116)

Characteristics	Total (n=116)		Recurrence (n=58)		Non recurrences (n= 58)		P value
	n	%	n	%	n	%	
Age (Years)							0.743
< 45	18	15.5%	8	13.8%	10	17.2%	
45-60	38	32.8%	18	31.0%	20	34.5%	
> 60	60	51.7%	32	55.2%	28	48.3%	
Mean ± SD	59.94	± 12.50	61.02	± 12.29	58.86	± 12.73	0.356
Gender							1.000
Male	66	56.9%	33	56.9%	33	56.9%	
Female	50	43.1%	25	43.1%	25	43.1%	
Underlying disease							
Hypertension	91/116	78.4%	42/91	46.2%	49/91	53.8%	0.114
Dyslipidemia	61/116	52.6%	32/61	52.5%	29/61	47.5%	0.577
Diabetes mellitus	82/116	70.7%	43/82	52.5%	39/82	47.5%	0.415
Smoking	54/116	46.6%	29/116	25%	25/116	21.6%	0.457
Alcohol drinking	9/116	7.8%	4/116	3.5%	5/116	4.3%	1.000
Type of RVO							0.636
CRVO	94	81.0%	48	82.8%	46	79.3%	
HRVO	22	19.0%	10	17.2%	12	20.7%	
Hyper reflective foci							0.011*
Yes	39	33.6%	26	44.8%	13	22.4%	
No	77	66.4%	32	55.2%	45	77.6%	
CST							
Mean ± SD	453.10	± 95.39	460.60	± 76.51	445.60	± 111.30	0.073
Median (min-max)	440.0	315-749	450.5	334-714	422.0	315-749	

P values for mean data were calculated with the use of independent t-test or Mann-Whitney U-test, for percentages with the use of Chi-square test or Fisher's exact test

The systolic mean blood pressure was found to be 145.07 ± 14.13 and 146.40 ± 13.90 in the recurrent and non-recurrent respectively. While the diastolic mean blood pressure was 81.57 ± 9.99 and 84.16 ± 8.87 for the recurrent and non-recurrent groups respectively. Furthermore, triglyceride levels are significantly higher in the recurrent than non-recurrent groups (115.12 ± 33.73 and 94.25 ± 29.99, P value <0.001) respectively. Similarly, HbA1c levels are significantly higher in the recurrent than non-recurrent groups (7.38 ± 1.02 and 6.64 ± 1.36, P value <0.007). (table 2)

Table 2: Association of Systemic and Ocular Risk Factors

	Recurrence			Non recurrences			P value
	n	Mean	± SD	n	Mean	± SD	
Blood pressure (mmHg)							
Systolic blood pressure	58	145.07	± 14.13	58	146.40	± 13.90	0.611
Diastolic blood pressure	58	81.57	± 9.99	58	84.16	± 8.87	0.154
Total cholesterol	28	223.50	± 45.29	25	220.92	± 50.40	0.845
Triglycerides	28	115.12	± 33.73	25	94.25	± 29.99	0.001*
FBS	44	162.02	± 22.10	40	151.95	± 42.62	0.172
HbA1c	42	7.38	± 1.02	38	6.64	± 1.36	0.007*
Baseline BCVA (ETDRS)	58	40.62	± 11.22	58	42.78	± 9.70	0.332

P values from independent t-test or Mann-Whitney U-test, * Significant at the 0.05 level

Furthermore, baseline visual acuity for patients with CRVO are similar in the recurrent and non-recurrent groups (40.33 ± 11.89 and 43.17 ± 10.35, P value 0.260) respectively. Of which, 54.2% in the recurrent group can see in the range of 31-49 ETDRS letters and 52.2% can see ≥ 50 ETDRS letters in the non-recurrent group. (table 3)

Table 3: Baseline visual acuity in retinal vein occlusion (n=116)

	Total (n=116)		Recurrence (n=58)		Non recurrences (n= 58)		P value
	n	%	n	%	n	%	
CRVO Group (n=94)							
ETDRS letter							0.166
≤30	10	10.6%	4	8.3%	6	13.0%	
31-49	42	44.7%	26	54.2%	16	34.8%	
≥ 50	42	44.7%	18	37.5%	24	52.2%	
Mean ± SD	41.72	± 11.19	40.33	± 11.89	43.17	± 10.35	0.260
HRVO Group (n=22)							
ETDRS letter							0.517
≤30	1	4.5%	1	10.0%	0	0.0%	
31-49	13	59.1%	5	50.0%	8	66.7%	
≥ 50	8	36.4%	4	40.0%	4	33.3%	
Mean ± SD	41.59	± 6.97	42.00	± 7.53	41.25	± 6.78	0.755

P values for mean data were calculated with the use of Mann-Whitney U-test, for percentages with the use of Chi-square test or Fisher's exact test

Discussion

The results of this study suggests that a significant proportion of retinal vein occlusion patients are aged above 60 years, making up 55.2% and 48.3% of the recurrent and non-recurrent groups respectively. Regarding gender, the proportion of patients with RVO were 56.9% and 43.1% for males and females, respectively. Furthermore, a significant majority of patients with RVO were found to have comorbidities of hypertension (78.4%), diabetes (70.7%) and dyslipidemia (52.6%), respectively. These findings were in line with previous literature regarding risk factors for retinal vein occlusions.[18]

An important finding is that triglyceride and HbA1c levels were found to be significantly higher in retinal vein occlusion patients with recurrent macula edema ($P<0.001$ and $P<0.007$, respectively). These findings support its pathogenesis of retinal vein occlusion including atherosclerosis of the artery and veins.[5]

Hyper-reflective foci are an important biomarker for the visual prognosis and treatment response of anti-VEGF in retinal vein occlusion with macula edema (figure1).[19] Some theories suggest that hyper-reflective foci are caused by inflammation processes as opposed to VEGF. Hence, the poor response of anti-VEGF treatment to certain types of macula edema and recurrence. This study demonstrates that 44.8% of patients in the recurrent macula edema group are found to have hyper-reflective foci on OCT Macula imaging, in line with previous studies.

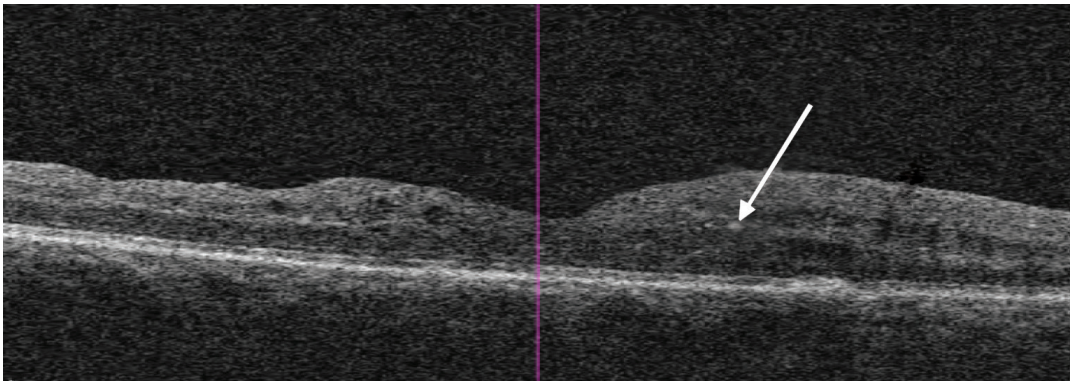

Figure 1: High-definition optical coherence tomography image through the fovea shows macular edema and hyper reflective retinal foci (white arrow).

Other factors contributing to the recurrence of macula edema in patients with RVO include higher levels of smoking (P value 0.457) and central subfield thickness at baseline (P value 0.073).

Visual acuity is a representation of the disease severity in retinal vein occlusions, which can also be a measure of response to treatment and prognostication for the chance of recurrence.[20-22] Our study found that initial BCVA was insignificantly lower in the recurrent group compared to the non-recurrent group (40.62 ± 11.22 vs 42.78 ± 9.70, P value 0.332) (table 2). This finding is thought to be due to the fact that the study used the Snellen visual acuity chart which was subsequently converted to the approximate ETDRS letter equivalent using an equation (approximate ETDRS letter score = 85+50 x log Snellen fraction).[23] Resulting in potential errors of the ETDRS letter scores used in the subgroup analysis. Our data suggested that baseline BCVA for both the central retinal vein occlusion (CRVO) and hemi-RVO patients were lesser in the recurrent group, ranging between 31-49 EDTS letters, compared to the non-recurrent group at ≥ 50 ETDRS letters (table 3). Nevertheless, there is a tendency for the non-recurrent group to have a better baseline visual acuity than the recurrent group, and further studies associating visual acuity and recurrence of macula edema in RVOs are warranted.

This study suggests that patients with RVO and macula edema who received Bevacizumab intravitreal anti-VEGF injections experienced the largest amounts of recurrence less than 6 months after treatment at 41.4%, with Ranibizumab following closely at 37% and Aflibercept at 24.1%. These findings may be in part due to the differing structures of the anti-VEGF drugs with subsequent binding affinities for VEGF which may affect the time to recurrence[24] (table 4). There is a tendency for Bevacizumab to have limited effectiveness compared to its counterparts, and this finding warrants further studies. Other limitations in this study include the lack of FA or OCT Angiogram due to the study's retrospective nature to identify the ischemic status of both clinical groups to help characterize the prognostic factors in recurrence of RVOs.

Table 4: Duration of Anti-VEGF in recurrence group

	Bevacizumab (n=58)		Ranibizumab (n=46)		Aflibercept (n=25)	
	n	%	n	%	n	%
Recurrence interval (n=62)						
< 6 months (n=29)	12	41.4%	11	37.9%	7	24.1%
≥ 6 months (n=33)	9	27.3%	14	42.4%	12	36.4%

Conclusion

Various factors contribute to the recurrence of macula edema in retinal vein occlusions, ranging from HbA1c, triglycerides which can contribute to the prognostication of the disease. Hypertension was not significantly more common in the recurrence group. Furthermore, baseline BCVA can help predict the responsiveness of the treatment and its likelihood of recurrence. Presently, biomarkers play an important role in predicting visual outcomes after completion of intravitreal anti-VEGF treatment. Hyper-reflective foci are associated with recurrence of macula edema in RVOs after treatment, in addition to a limited treatment response to Bevacizumab compared to other anti-VEGFs. Nevertheless, long term studies are warranted to observe long term macula edema resulting in irreversible tissue damage and its effects on visual outcome and correlation to changes seen on OCT macula for the purpose of furthering treatment benefits of the patient.

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