Ibrahim Khairul-Anwar[1,2,3], Rosli Abdul-Hadi[1,2,3], Hassan Mutasim[1,4], Embong Zunaina[1,2,*]

[1]Department of Ophthalmology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia,16150 Kubang Kerian, Kelantan, Malaysia.

[2]Hospital Universiti Sains Malaysia, Jalan Raja Perempuan Zainab II, 16150 Kubang Kerian, Kelantan, Malaysia.

[3]Department of Ophthalmology, Kuliyyah of Medicine, International Islamic University Malaysia, Kuantan Campus, Bandar Indera Mahkota, 25200 Kuantan, Pahang.

[4]Department of Ophthalmology, Faculty of Medicine, Al Neelain University, 11111, PO Box 84, Khartoum, Sudan.

Clinical Profile of Retinal Vein Occlusion in Hospital Universiti Sains Malaysia – 7 Years Review

***Abstract*—** To review the clinical profile of retinal vein occlusion (RVO) in Hospital Universiti Sains Malaysia (USM) from 2011 until 2017. This was a retrospective single-centre case series. The medical records of the patients presented to Ophthalmology Clinic with RVO from 2011 to 2017 were reviewed. A total of 24 patients (26 eyes) with a diagnosis of RVO in Hospital USM were reviewed. There was 91.6% of our patients were aged more than 45 years old with predominantly affected male gender (58.3%). Majority of the patients were Malays (87.5%). Hypertension (70.8%), hyperlipidemia (70.8%) and diabetes mellitus (54.2%) were the common systemic comorbidities in RVO patients. Majority of the patients (87.5%) were non-smoker. Based on type of RVO, there were 38.5% central RVO, 26.9% branch RVO, 19.2% macular branch RVO, and 15.4% hemivein occlusion. RVO was bilateral in 2 patients (8.4%). Based on fundus fluorescein angiography, 3 patients (11.5%) showed ischaemic features. Reduce vision (91.6%) was the main presenting symptoms of RVO while intraretinal haemorrhage (100%) and macular oedema (96.2%) were the most common ocular signs found in RVO. There were 16 eyes (61.5%) have visual acuity equal or better than 6/60 at presentation. Patient who had visual acuity equal or better than 6/60 showed promising improvement in visual acuity post treatment. Elderly with multiple comorbidities complaining of worsening of vision should have high index suspicion of RVO. Presenting visual acuity is associated with final visual outcome post treatment.

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*Corresponding author:
Embong Zunaina
E-mail: zunaina@usm.my

1 INTRODUCTION

Retinal vein occlusion (RVO) is a common vascular disorder of the retina and one of the most common causes of vision loss worldwide [1,2]. Specifically, it is the second most common cause of blindness from retinal vascular disease after diabetic retinopathy [1]. RVO is estimated to affect between 0.3% and 2.1% of the global population [3-5].

RVO is due to an interruption of the normal venous drainage from the retinal tissue. Classification of RVO is depending on the site of occlusion. Occlusion of the central retinal vein at the level of the optic nerve is known as central retinal vein occlusion (CRVO). Occlusion at the primary superior branch or primary inferior branch involving approximately half of the retina is referred to hemiretina vein occlusion (HRVO). Meanwhile, obstruction at any more distal branch of the retinal vein is known as branch retinal vein occlusion (BRVO) [6].

BRVO is divided into two distinct entities: major BRVO and macular BRVO. In major BRVO, one of the major branch retinal veins is occluded. Whereas macular BRVO refers to occlusion of macular venules [6,7]. Major BRVO involves the superior temporal quadrant in 65% of eyes and the inferior temporal quadrant in 31% [8]. For macular BRVO, 81% of eyes involved superior macular region and 19% in inferior macular region [8]. The location of the occlusion influences the pathogenesis, clinical presentation, and management of RVO. RVO is further subdivided into non-ischaemic and ischaemic types according to the amount of retinal capillary ischaemia seen on fluorescein angiography [7].

Clinical features of RVO include dilated and tortuous retinal veins, deep and superficial retinal haemorrhages, cotton wool spots, and retinal oedema [7]. In CRVO, these features are found in all quadrants of the retina. Unlike CRVO, retinal haemorrhages corresponding to the sector of retina involved are characteristic features of BRVO [7]. Visual loss in RVO commonly occurs as a result of macular oedema or macular ischaemia, and in more advanced stages, it is due to vitreous haemorrhage [3].

RVO is thought to result from a thrombotic event or vessel wall pathology. Hypertension, diabetes mellitus, atherosclerosis, hyperlipidemia, smoking and glaucoma are the major risk factors for the development of RVO in older patients [9]. Hypercoagulability and vasculitis are the important risk factors for the development of RVO in younger patients [10,11].

In general, the aims of investigations are to identify and treat the causative factors, and to prevent progression or prevent recurrence in the same eye or in the fellow eye. RVO Guideline published by The Royal College of Ophthalmologist state that the main benefit of medical tests in RVO is to improve health by treating the commonly associated risk factors such as atherosclerosis, hypertension, diabetes and lipid abnormalities [12].

Fluorescein angiography is a procedure that able to document the degree of obstruction, the severity of the capillary permeability alterations, and the extent of the retinal capillary nonperfusion. Optical coherence tomography (OCT) is useful in the assessment of macular oedema particularly in monitoring its course. Detection of hyperreflective line located in the outer plexiform layer by OCT is a sign of acute ischaemia [13]. In chronic phase of CRVO, OCT might show inner layer loss of the retina.

Current therapeutic options for the treatment of macular oedema secondary to RVO include laser photocoagulation, vascular endothelial growth factor (VEGF) inhibitors, and intraocular steroids [14]. Anti-VEGF therapy is now the standard treatment and is effective for RVO-related macular oedema in most cases [15].

2 METHODS

This was a retrospective single-centre case series of RVO in Ophthalmology Clinic of Hospital Universiti Sains Malaysia (USM) from 2011 until 2017. Hospital USM is a tertiary referral centre and one of the teaching hospitals at the east coast region of Peninsular Malaysia.

In this retrospective study, we reviewed the medical records of patients presented to Ophthalmology Clinic with RVO. All clinical data were collected in a confidential manner which include demographic data, systemic comorbidities, laboratory profile, ocular profile and treatment modality. OCT and fundus fluorescein angiography (FFA) were the tools that used for ocular assessment in this review of case series.

Decision of treatment were given based on the severity of RVO, presence of macular oedema and presence of neovascularisation. Treatment modalities that were performed in this review of case series include intravitreal anti-VEGF and laser therapy.

The consent was obtained from the Director of Hospital USM on behalf of all patients. This review of case series was conducted in accordance to Declaration of Helsinki for human research, registered under Research Registry. The patient's personal identification and clinical data were kept confidential, and data were reported as collective information.

3 RESULT

There were 24 patients (26 eyes) diagnosed with RVO in Ophthalmology Clinic during 7 years period from 2011 until 2017. The demographic data of the patients at time of diagnosis is illustrated in Table 1. About 91.6% patients were more than 45 years old with predominantly affected male gender (58.3%). Majority of the patients were Malays (87.5%) and only 3 (12.5%) Chinese patients. There were only 3 (12.5%) patients reported smoking and the remainder 21 (87.5%) patients were non-smoker.

Majority of the patients who were diagnosed with RVO had associated medical comorbidities; hypertension (70.8%), hyperlipidemia (70.8%) and diabetes mellitus (54.2%). The RVO patients that have hyperlipidemia, all of them had high blood cholesterol level (> 6.3 mmol/L). Among the RVO patients with hyperlipidemia (17 patients), 6 patients had only hypertension and 8 patients had both hypertension and other comorbidities. There were 1 patient had only diabetes mellitus and 2 patients had no comorbidity.

Table 1: Demographic data, systemic comorbidities and laboratory profile of patients with retinal vein occlusion (n = 24 patients).

Variable		Frequency (n)	Percentage (%)
Demographic Data			
Age (year)			
Mean	59.5		
Range	41–78		
Age group			
≤ 45		2	8.4%
> 45		22	91.6%
Gender			
Male		14	58.3%
Female		10	41.7%
Race			
Malay		21	87.5%
Chinese		3	12.5%
Smoking status			
Yes		3	12.5%
No		21	87.5%
Systemic Comorbidities			
Hypertension		17	70.8%
Hyperlipidemia		17	70.8%
Diabetes mellitus		13	54.2%
Heart disease		3	12.5%
CVA		1	4.2%
Laboratory Profile			
Cholesterol (mmol/L)			
≤ 6.3		7	29.2%
> 6.3		17	70.8%
Triglyceride (mmol/L)			
≤ 1.6		2	8.3%
> 1.6		7	29.2%
Missing data		15	62.5%
Fasting blood glucose (mmol/L)			
≤ 6.6		11	45.8%
> 6.6		13	54.2%

Abbreviation: CVA: Cerebrovascular accident

In terms of ocular clinical profile (Table 2), the most common ocular symptoms at presentation were blurred vision (91.6%). Double vision (4.2%) and central scotoma (4.2%) were less common ocular presentation. Most of the patients had insidious onset in which 11 (45.9%) patients had duration of symptom for more than one-month.

Out of 24 patients, 22 patients (91.6%) had unilateral involvement and the other 2 patients (8.4%) involved bilateral eyes. Those with bilateral involvement, one patient has left eye CRVO and right eye BRVO. The second patient has bilateral HRVO.

A total of 26 eyes (100%) were found to have retinal haemorrhages in form of dot haemorrhages, blot haemorrhages, and flame-shape haemorrhages. Only 8 eyes (30.8%) have cotton wool spot. There were 25 eyes (96.2%) showed features of macular oedema and confirmed by OCT assessment. Two eyes (7.7%) were found to have retinal neovascularisation and 1 eye (3.8%) has iris neovascularisation at the time of presentation. Based on the type of RVO, CRVO was the commonest type which account 38.5%, followed by BRVO (26.9%), macular BRVO (19.2%) and HRVO (15.4%).

Table 2: Clinical ocular profile and ocular assessment of patients with retinal vein occlusion.

Variable	Frequency (n)	Percentage (%)
Clinical Ocular Profile		
Ocular Presentation (n = 24 patients)		
Presenting symptom		
Reduce vision	22	91.6%
Double vision	1	4.2%
Central scotoma	1	4.2%
Duration of symptom		
Less than 1 week	8	33.3%
1 week -1 month	5	20.8%
More than 1 month	11	45.9%
Ocular signs (n = 26 eyes)		
Intraretinal haemorrhage	26	100%
Cotton-wool spot	8	30.8%
Swollen disc	3	11.5%
Iris neovascularisation	1	3.8%
Retinal neovascularisation	2	7.7%
Macular oedema	25	96.2%
Type of RVO		
Central RVO	10	38.5%
Branch RVO	7	26.9%
Macular branch occlusion	5	19.2%
Hemivein occlusion	4	15.4%
Laterality		
Unilateral	22	91.6%
Bilateral	2	8.4%
Ocular Assessment (n = 26 eyes)		
FFA		
Ischaemic	3	11.5%
Non-ischaemic	8	30.8%
FFA not done	15	57.7%
OCT		
Macular oedema	25	96.2%
No macular oedema	1	3.8%

FFA was performed to classify the RVO into ischaemic or non-ischaemic type. Unfortunately, only 11 out of 24 patients were underwent FFA assessment due to logistic problem and some of the patients had unstable medical condition. Out of 11 patients who underwent FFA, only 3 eyes (27.3%) were classified into ischaemic type. Overall ischaemic RVO were 5 eyes; 2 eyes showed presence of retinal neovascularisation, 2 eyes evidenced by FFA, and 1 eye has both in which there was presence of iris neovascularisation and evidenced by FFA. RVO with ischaemic features tend to have marked and

extensive retinal haemorrhages compared to non-ischaemic RVO.

At presentation, 16 eyes (61.5%) showed best corrected visual acuity (BCVA) equal or better than 6/60 while the remaining 10 eyes (38.5%) had BCVA worse than 6/60. All RVO patients with macular oedema (25 eyes) received the treatment provided either anti-VEGF monotherapy or combination of anti-VEGF and laser therapy. Nine eyes (36.0%) were treated with anti-VEGF monotherapy and 16 eyes (64.0%) received combination of anti-VEGF and laser therapy. Out of 16 eyes that received combination anti-VEGF and laser therapy, PRP was performed in 13 eyes and grid laser in 3 eyes. Pan retinal photocoagulation (PRP) was performed in 5 eyes with ischaemic RVO and 8 eyes in non-ischaemic type that showed features of impending ischaemic RVO. Three eyes were treated with additional grid laser for macular oedema due to unstable medical condition for continuation of anti-VEGF. Only 1 eye with a diagnosis of non-ischaemic BRVO without macular oedema was treated conservatively. The detail regarding the type of treatment received and BCVA post treatment were summarised in Table 3.

Table 3: Visual outcome and treatment modality for RVO (n = 25 eyes).

Presenting BCVA	n (%)	Treatment	n (%)	BCVA post treatment	n (%)
Equal or better than 6/60	15 (60.0%)	Anti-VEGF Mono-therapy	5 (33.3%)	Equal or better than 6/60	4 (80.0%)
				Worse than 6/60	1 (20.0%)
		Combination Anti-VEGF and PRP	7 (46.7%)	Equal or better than 6/60	5 (71.4%)
				Worse than 6/60	2 (28.6%)
		Combination Anti-VEGF and Grid laser	3 (20.0%)	Equal or better than 6/60	3 (100%)
				Worse than 6/60	0 (0%)
Worse than 6/60	10 (40.0%)	Anti-VEGF Mono-therapy	4 (40.0%)	Equal or better than 6/60	1 (25.0%)
				Worse than 6/60	3 (75.0%)
		Combination Anti-VEGF and PRP	6 (60.0%)	Equal or better than 6/60	1 (16.6%)
				Worse than 6/60	5 (83.4%)

Abbreviation: BCVA: Best corrected visual acuity; VEGF: Vascular endothelial growth factor

Post treatment at latest follow-up (26 eyes), 15 eyes (57.7%) had BCVA equal or better than 6/60 and 11 eyes (42.3%) had BCVA worse than 6/60. Out of 11 eyes with BCVA worse than 6/60, 8 of them had BCVA worse than 6/60 at presentation. Poor visual outcome post treatment was due to complication that arise from the disease which include formation of macular scar / atrophy (2 eyes), progression of disease into neovascular glaucoma (2 eyes) and formation of vitreo-macular traction (1 eye).

4 DISCUSSION

Our review showed that advancing age and systemic comorbidities are the common risk factors for RVO. The mean age was 59.5 years and 91.6% of our patients were above 45 years old. Our mean age of RVO is consistent with finding of previous studies [16,17]. Singapore Malay Eye Study (SiMES) [4] reported that the prevalence of RVO older than 40 years was 0.7% and 1.2% in the Beijing Eye Study [18].

In our review, we found that the distribution of RVO among the sample population were 87.5% and 12.5 % for Malay and Chinese races respectively. There was no significant difference in the age-standardized prevalence of RVO across the 3 ethnic groups (Malay, Chinese and Indian) in Singapore [19]. The differences between races in our study reflect local racial distribution. We also found that RVO was more common in male (58.3%) compared to female (41.7%). However, study done by Lim et al [4] reported that the frequency of RVO was higher in women than in men.

Systemic hypertension and hyperlipidemia were found in 70.8% of the patients which pose the major risk factors of RVO in our study. Association of systemic hypertension with RVO is comparable with study done by Shin et al [20] which reported 70.2% and 78.2% by Chen et al [17]. However, the percentage of hyperlipidemia is higher in our review compared to previous studies [16,17]. They reported the percentage of hyperlipidemia was 48.0-49.7%.

Diabetes mellitus, heart diseases and stroke were diagnosed among our RVO patients and estimated as 54.2%, 12.5% and 4.2% respectively. Diabetes mellitus is known as a risk factor for RVO [21]. Our review showed that the percentage of diabetes mellitus is slightly higher compare to Chen et al (39.6%) [16]. Meanwhile, percentage of heart disease and stroke were lower than population-based cohort study that

conducted in Taiwan (35.7 % and 23.9% respectively) [17].

Patients presented with RVO have a range of symptoms depending on the site and severity of occlusion. Typically, patients presented with sudden painless vision loss or visual field defect. Rarely, patients presented with floaters that resulted from vitreous haemorrhage. In our review, we found that 91.6% of our patients presented with reduced vision.

RVO demonstrated fundus features of superficial or deep retinal haemorrhages, cotton-wool spots, venous dilatation, and venous tortuosity [7,15]. In our review, we found that all patients (100%) presented with intraretinal haemorrhages and 96.2% with macular oedema. There were 7.7% presented with retinal neovascularisation and 3.8% with iris neovascularisation. Study done by Teoh & Amarjeet [22] reported higher percentage of retinal neovascularisation (26.3%) and iris neovascularisation (10.5%).

RVO was classified into CRVO or BRVO according to the site of occlusion. We found that the percentage of CRVO was higher compared to BRVO (38.5% versus 26.9%). In contrast with study done by Chen et al [16] which reported that BRVO was higher than CRVO (68.7% versus 31.3%).

Fluorescein angiography is a procedure that able to document the degree of obstruction, the severity of the capillary permeability alterations, and the extent of the retinal capillary nonperfusion [6,7]. In our review, only 11 out of 24 patients underwent FFA assessment. This is due to logistic problem and some of the patients had unstable medical condition that relative contraindicated to perform the procedure.

Current therapeutic options for the treatment of macular oedema secondary to RVO include laser photocoagulation, VEGF inhibitors, and intraocular steroids [14]. Anti-VEGF therapy is now the standard treatment and is effective for RVO-related macular oedema in most cases [15]. The landmark study such as BRAVO and CRUISE study showed the use of anti-VEGF leads to rapid improvement in visual acuity and macular oedema following BRVO and CRVO respectively [23,24]. COMRADE C study also demonstrated superiority of anti-VEGF over dexamethasone in patients with macular oedema secondary to CRVO, with lesser incidence of ocular adverse effect such as cataract and raise intraocular pressure [25]. Patient with unstable medical condition or has relative contraindication for anti-VEGF injection, grid laser is the treatment of option for macular oedema [26]. PRP should be given in CRVO patient that developed neovascularisation evidence by presence of new vessels in iris or angle. While BRVO patient should receive sectorial PRP to prevent the development of neovascularisation [26]. Chances of conversion of non-ischaemic CRVO to ischaemic CRVO was 12.6% within 18 months from the onset of non-ischaemic CRVO [27].

The visual acuity was used as a parameter to evaluate the improvement or worsening of eyes with RVO in our study. We found that patients that presented with BCVA equal or better than 6/60 and treated with either anti-VEGF monotherapy or combination therapy showed improvement in visual acuity. The group of patients with BCVA worse than 6/60 did not show great benefit from monotherapy of anti-VEGF or combined therapy. The improvement of visual acuity following the use of anti-VEGF was consistent with findings of other previous study [28-30].

5 CONCLUSION

Elderly with multiple comorbidities complaining of reduce vision should have high index suspicion of RVO. Presenting visual acuity is associated with final visual outcome post treatment. Delay in detection and management will cause worsening of vision and lead to irreversible ocular damage that will increase the social and financial burden to the society.

6 CONFLICT OF INTEREST

The authors have no conflicts of interest in this study.

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