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# Risk factor for retinal vein occlusion: A case control study

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**ABSTRACT**

**Purposes:** Retinal vein occlusion (RVO) is a major cause of vision loss. Its pathogenesis is still not completely understood. Our aim was to describe patients with RVO, to precise risk factors responsible to retinal vasculopathy in our population and to assess the prevalence of thrombophilia disorders patients with RVO, compared to population-based group of age- and sex-matched controls.

**Patients & methods:** Our study was retrospective conducted from 1 January 2013, until 30 June 2019, including 57 patients with RVO compared to 105 controls patient's age- and sex-matched free of any visual disorders. Among 57 RVO cases, 26 were men and 31 were women.

**Results:** The mean age was 45.0±14.7 years. Among systemic and ocular risk factors for RVO we found hypertension in 12 patients (31.6%), dyslipidemia in four patients (10.5%), diabetes in four patients (10.5%), and smoking in six patients (16.2%). Three patients (9.7%) had glaucoma and two patients (6.5%) had diabetic retinopathy. Ophthalmology examination found unilateral RVO in 52 patients (91.0%) and bilateral RVO in five patients (11.1%). Retinal angiography showed ischemic signs in seven patients (18.4%). Non-ischemic RVO was retained in 31 cases (81.6%). Macular edema was present in 12 patients (38.7%). Six cases (19.4%) developed neovascular glaucoma and two cases (6.5%) presented reversible blindness. Measures of thrombophilia practiced in 57 patients revealed 13 abnormalities (22.8%): Isolated thrombophilia disorder in 11 patients (71.4%) and combined prothrombotic disorder in two others.

**Conclusions:** Among systemic and ocular risk factors for RVO, we found hypertension in 12 patients (31.6%). Thrombophilia disorders were also common.

**Keywords:** retinal vein occlusion, risk factor, thrombophilia, hypertension

## INTRODUCTION

Retinal vein occlusion (RVO) is a major cause of vision loss [1]. It represents the second most common retinal vascular disorder in the world after diabetic retinopathy [2]. Three types of RVO were identified: branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), and hemi-CRVO with involvement of only one half of retina surface. BRVO is four to six times more prevalent than CRVO [3]. Its pathogenesis is still not understood. The combination of venous stasis, degenerative changes on vessel wall, and blood hypercoagulability (known as Virchow's triad) were responsible in the occurrence of RVO [4]. Many ocular and systemic factors including glaucoma, high blood pressure, dyslipidemia, diabetes mellitus and smoking [5, 6] were described to be risk factors to the development of RVO. In the other hand, the role of prothrombotic disorder in the pathogenesis of RVO is controversial [7-9]. An etiological exploration is justified. Our aim was to describe patients with RVO, to precise risk factors responsible to retinal vasculopathy in our population and to assess prevalence of thrombophilia disorders patients with RVO, compared to population-based group of age- and sex-matched controls.

## PATIENTS & METHODS

Our study was retrospective conducted from 1 January 2013 until 30 June 2019, including 57 patients with RVO compared to 105 control patient's age- and sex-matched free of any visual disorders. Control patients had no previous venous or arterial thrombotic events.

The research was conducted according to the principles of the Declaration of Helsinki. At each case, data were gathered using a specified questionnaire with a focus on cardiovascular events, hypertension, diabetes, cigarette smoking, estrogen-containing oral contraceptives hyperlipidemia and thrombophilia disorders. No cases had taken anticoagulant within three months of blood sampling. One or more months after their RVO, serologic coagulation assays were done. Serologic measures of thrombophilia included anticardiolipin (aCL) antibodies, antigenic protein C(PC), antigenic protein S (PS), antithrombin III, resistance to activated protein C (RaPC)

**Table 1.** Risk factors of retinal vein occlusion

| | Patients | Témoins | p-value |
|---|---|---|---|
| Hypertension | 12 (31.6%) | 6 (5.9%) | **$<10^{-3}$** |
| Hyperlipemia | 4 (10.5%) | 1 (1.0%) | **0.019** |
| Diabetesmellitus | 4 (10.5%) | 5 (4.9%) | 0.254 |
| Smoking | 6 (16.2%) | 9 (8.8%) | 0.226 |
| Oestroprogestatifs | 1 (2.6%) | 1 (1.0%) | 0.463 |
| Behcet's disease | 1 (3.8%) | 2 (1.9%) | 1.000 |
| Facteur V Leiden mutation | 8 (14.0%) | 7 (6.8%) | **$<10^{-3}$** |
| Mutation facteur II mutation | 0 (0.0%) | 1 (1.0%) | 1.000 |
| MTHFR mutation | 4 (30.8%) | 23 (22.5%) | 0.474 |

**Table 2.** Risk factors of RVO dispatched by age group

| | Patients <50 ans | Controls <50 ans | Patients ≥50 ans | Controls ≥50 ans |
|---|---|---|---|---|
| Hypertension | 7 (26.9%) | 4 (47.0%) | 5 (41.7%) | 2 (11.8%) |
| | p=0.012 | | p=0.006 | |
| Hyperlipidemia | 1 (3.8%) | 0 (0.0%) | 3 (25.0%) | 1 (5.9%) |
| | p=0.236 | | p=0.274 | |
| Diabetesmellitus | 3 (11.5%) | 1 (11.8%) | 1 (8.3%) | 4 (23.6%) |
| | p=0.143 | | p=1.000 | |
| Smoking | 3 (12.0%) | 9 (10.6%) | 3 (25.0%) | 0 (0.0%) |
| | p=0.712 | | p=0.274 | |
| Contraception | 1 (4.0%) | 1 (1.8%) | 0 (0.0%) | 0 (0.0%) |
| | p=0.408 | | p=0.463 | |
| Behcet's disease | 1 (5.0%) | 2 (2.3%) | 0 (0.0%) | 0 (0.0%) |
| | p=0.408 | | p=1.000 | |
| Factor V Leiden mutation | 2 (5.5%) | 6 (7.1%) | 6 (28.6%) | 1 (5.8%) |
| | p=1.000 | | p=0.098 | |
| Factor II mutation | 0 (0.0%) | 1 (1.2%) | 0 (0.0%) | 0 (0.0%) |
| | p=1.000 | | | |
| C677T MTHFR mutation | 3 (50.0%) | 21 (24.7%) | 1 (14.3%) | 2 (11.7%) |
| | p=0.336 | | p=1.000 | |

and lupus anticoagulant (LA). Factor V G1691A (factor V Leiden), G20210A prothrombin and MTHFR C677T mutation, were performed in cases with RVO and in healthy controls.

Statistical analysis was performed using SPSS software (version 20). The Chi-square test was used to compare qualitative variables or frequencies and the student test for the comparison of quantitative variables. A p-value≤0.050 was considered statistically significant.

## RESULTS

Among 57 RVO cases, 26 were men and 31 were women. The incidence of RVO was eight cases/year [range six to 11 per year]. The mean age was 45.0±14.7 years [20-75 years]. 36 patients (63.2%) were under 50 years old. Symptoms leading to diagnosis were poor visual acuity in 27 cases, blurry vision in 17 cases, seven had transient visual obscuration and four had ocular pain. One patient had no symptoms. Ophthalmological examination found unilateral RVO in 52 patients (91.0%) and bilateral RVO in five patients (11.1%). Retinal angiography showed ischemic signs in seven patients (18.4%). Non-ischemic RVO was retained in 31 cases (81.6%). Macular edema was present in 12 patients (38.7%). Six cases (19.4%) developed neovascular glaucoma.

Among systemic and ocular risk factors for RVO, we found hypertension in 12 patients (31.6%) versus six controls (5.9%), dyslipidemia in four patients (10.5%) versus one control (1.0%), diabetes in four patients (10.5%) versus five controls (4.9%), smoking in six patients (16.2%) versus nine controls (8.8%); one case taking estrogen-progestins contraception versus one control (1.0%) and Behcet's disease in one patient (3.8%) versus two controls (1.9%). Three patients (9.7%) had glaucoma and two (6.5%) had diabetic retinopathy. Cardiovascular exploration including electrocardiogram was performed in 28 patients (49.1%) revealing tachycardia in two patients (7.1%) and bradycardia in one patient (3.6%). One case had mitro-aortic valve pathology on the diagnosis of RVO.

The distribution of all Risk factor in patients and controls is shown in **Table 1**. Statistical analysis showed that hypertension was significantly more associated with RVO in both patients less than 50 years old (p=0.012) and in patients between 50 to 75 years (p=0.060) (**Table 2**). Thus, the role of hypertension in the occurrence of RVO was evident in both groups (**Table 1**). Hyperlipemia was also significantly correlated with presence of RVO (p=0.019). Statistical analysis did not find any significant correlation for diabetes, smoking or estrogen intake to increase the risk for development of RVO.

Measures of thrombophilia practiced in 57 patients and compared to healthy patients revealed 13 abnormalities (22.8%): 11 cases of isolated thrombophilia disorder and combined prothrombotic disorder in two others. Congenital thrombophilia abnormalities observed were factor V Leiden mutation (n=6), MTHFR C677T mutation (n=3), PS deficiency (n=2; 3.5%), association of PS deficiency–factor V Leiden mutation (n=1) and the combination of factor V Leiden mutation–MTHFR C677T mutation in one case (**Table 3**). Then we retain: PS deficiency (n=3; 5.2%), resistance to activated protein C (RPCa) (n=7; 12.8%) with a median of 70s [66s-86s], factor V Leiden mutation (n=8; 14.0%) with heterozygous polymorphism (GA) (n=7) and homozygous appearance (n=1) and MTHFR C677T mutation (n=4) with heterozygous profile.

**Table 3.** Thrombophilia disorders observed in our study

| | Thrombophilicdisorder | Number of cases (%) |
|---|---|---|
| Isolateddisorder | PS deficiency | 2 (3.5%) |
| | MTHFR C677T mutation | 3 (5.2%) |
| | Factor V Leiden mutation | 6 (10.5) |
| Combineddisorders | PS deficiency+factor V Leiden mutation | 1 (1.7%) |
| | Factor V Leiden mutation+MTHFR C677T mutation | 1 (1.7%) |

**Table 4.** Incidence of resistance to activated protein C in patients with RVO in different studies

| Study | Number of patients | Resistance to activated protein C (%) |
|---|---|---|
| [23] | 55 | 3.6 |
| [24] | 44 | 19.0 |
| [28] | 31 | 36.0 |
| [29] | 24 | 25.0 |
| Our study | 57 | 12.6 |

We did not find antithrombin deficiency, PC deficiency or prothrombin mutation. LA was detected in 50 patients, anti-β2GPI and anticardiolipin antibodies detected in 19 patients were all negatives. Control population presented factor V Leiden mutation in 6.8% of cases and MTHFR C677T mutation in 23 cases (22.5%). Thrombophilia disorder had no significant difference between male and female gender in our population study. A significant correlation was found between factor V Leiden mutation and the occurrence of RVO (p=0.040). There is no significant correlation according to the site of occlusion (p>0.050). Among the 24 files of patients in whom data of therapy was available, anti-platelet agent was started in 17 patients (51.5%), laser treatment was used in five patients (15.2%), intra-vitreal corticosteroid in two cases (6.1%) and intra-vitreal anti-VEGF injections in nine patients (27.3%). Progress showed improvement in three patients (13.0%), worse outcomes in two patients (8.7%) (one patient had vitreous hemorrhage) and 13 patients (56.6%) were lost to follow-up. Data were absent in 34 patients.

## DISCUSSION

RVO like others venous-thromboembolism disorder being multifactorial in their origin. The role of systemic vascular diseases, metabolic diseases, and thrombophilia risk factors in RVO were largely reported and was still controversial. Two Tunisian studies reported the role of factor V Leiden mutation, the G20210A mutation and the MTHFR C677T mutation in the occurrence of RVO [10, 11]. Other studies showed conflicting results.

In our study, 31.6% of our population presented hypertension like results (30.0%) in [6]. Hypertension is considered as a risk factor in the occurrence of RVO like the literature data. This finding was significant regardless the age group (p<0.050). Its presence was noticed in more than 80.0% of cases according to the meta-analysis in [12]. Dyslipidemia was also considered a risk factor in RVO's disease. In literature, its role remains unclear. Some studies have shown an important association between hypercholesterolemia and RVO [13].

In the other hand, we found that thrombophilia disorders were present in 22.8% of patients more than other frequency of other studies (10.0%) [14], and lower than observed in patients with deep vein thrombosis (24.0-37.0%) [15-22]. 5.2% of patients had PS deficiency, similarly to [18] (4.0%) and [22] (5.0%). These studies and ours did not find a significant correlation between this congenital deficiency and RVO [9, 17-19]. PC deficiency was not present in our population like the case in [20]. The percentage of patients with PC deficiency was respectively at 2.5% and 1.2% without any significant correlation in [21, 22]. It was found that 20.0% of cases presented PC deficiency [18].

Our study found that AT deficiency was not observed [23]. A meta-analysis including 14 studies, whose purpose was to detect the markers of thrombophilia in the pathogenesis of RVO, found no correlation between AT deficiency and RVO [24]. The most significant finding in our study was to have greater prevalence of factor V Leiden mutation in patients with RVO than controls. Resistance to activated protein C (12.3%) was the most prevalent condition to the occurrence of RVO. Other recent studies reported the same results [3.6% to 36.0%] [23-29] (**Table 4**). A meta-analysis including 17 studies directed by European authors revealed 7.7% of patients with RVO had RaPC and it was significantly higher in patients than in controls suggesting its role in the pathogenesis of RVO [25].

Recent studies were rather directed to show the role of polymorphism factor V Leiden in the occurrence of RVO. In fact, it reflected the genetic confirmation of RaPC, which consists of the replacement of adenine by guanine at the position G1691A of factor V [10]. It represents the most common disorder in hereditary thrombophilia (4.0-7.0% of the general population) [13].

In our population, we detected the G1691A factor V Leiden mutation in 14.0% of cases of which 12.3% were heterozygous GA genotype and only 1.7% had a homozygous AA genotype. It was also reported a 13.0% frequency of factor V Leiden [24]. The study guided by Tunisians [10] reveals that factor V Leiden mutation was present in 47.7% of patients with RVO. Thus, a statistically significant relationship between this genetic disorder and the disease has been proven ($p<10^{-3}$). Our results were consistent with those of the meta-analyze in [21] including 18 studies and 1,748 patients, revealing a significant link between factor V Leiden polymorphism and RVO: odds ratio [OR]=1.66 95% CI: [1.19-2.32] [25]. Another meta-analysis including 37 studies and 2,510 patients, confirmed this association [26]. In a recent metanalysis, the authors found among 3,981 patients with RVO, the pooled prevalence of factor V Leiden mutation was 6.0%. Significant heterogeneity was found between geographical groups (p=.016), with the higher prevalence reported in Middle East/north African studies [27]. Although the increased prevalence of factor V Leiden mutation in patients presenting RVO compared to controls [10, 17, 20, 24], a significant association was less

**Table 5.** Case-control studies of C677T-MTHFR mutation in occurence of RVO

| | MTHFR (%) | C677T MTHFR polymorphism |
|---|---|---|
| [17] | 30.0 | Signifiant association (p=0.040) |
| [33] | 49.0 | No association |
| [34] | 51.0 | No association |
| [35] | 45.7 | No association |
| [36] | 71.0 | No association |
| [37] | 38.1 | Signifiant association (p<0.005) |
| Our study | 7.0 | No association |

frequent [10,17]. Some studies [6, 9] did not support the role of such association. The presence of factor V Leiden was not affected by age like the study in [7]. Others highlighted the occurrence of this disorder in patients with RVO aged less than 50 years [22, 24]. Dispatching of this disorder according to age did not show any significant difference and this could be explained by the low number of our population. The important occurrence of RVO in the population without classic risk factors was also founded in [7] defining an increased risk at 1.6 more times to have factor V Leiden mutation in patients without classic risk factors of RVO than in people with these conventional risk factors [25].

Factor II G20210 mutation was the second hereditary prothrombotic disorder present in 2.0% of population [13]. Although this disorder did not be observed in our series, its association with thromboembolic disease was already established [30]. Other series found similar results than ours [6, 22, 31]. Two metanalysis confirmed the absence of correlation between G20210A mutation and RVO [30, 31]. It was confirmed that the significant correlation of this disorder with RVO [10].

About the C677T MTHFR mutation, our findings revealed that 7.0% of patients had this mutation on its heterozygous profile without significant correlation. A new Spanish study discovered an increased prevalence ofC677T MTHFR mutation (85.3%) without important difference comparing to control subjects (88.1%) [31-36] (**Table 5**).

Anti phospholipid anti bodies (aPL) were negative in all like in [28]. In [13], 5.0% of patients had positive Apl antibodies. Data were controversial. In fact, in a study including 313 patients, we did not find correlation between aPL statue and RVO's occurrence (p=0.736) [6] unlike another one in which the correlation was evident [22].

16.7% of our population presented combined disorder similarly to a German study in which the frequency was at 18.0% [37]. In our study the association of G1691A factor V polymorphism and polymorphism C677T MTHFR was diagnosed in a 20-year female without any risk factor of RVO. This association was observed in [17, 38]. The second patient had 21 years presented PS deficiency in combination with factor V Leiden mutation. These results were concordant with the German study concluding that the combination of many prothrombotic disorders in young people represent a risk factor to develop RVO [37].

This study has some limitations. It is a monocentric retrospective study and probably Homocysteine levels should have been evaluated in the whole study group to derive a significant relationship between homo-cysteinemia and RVO, but this test is not available in our department. The size of our sample of 57 RVO cases is relatively small but is like many other studies in literature.

However, our study has some strengths. First, we performed analysis of cardiovascular risk and genetic thrombophilia tests in patients and controls groups. Second, our patients have long-term follow-up. Third, we have compared data from RVO studies and studies on healthy population of different geographic areas, including our own.

## CONCLUSIONS

In summary, in all patients with RVO, vascular risk should be adjusted toward the most optimal levels, correcting those factors susceptible to be treated, according to the current guidelines and promoting smoking cessation. In young patients without cardiovascular risk, screening for thrombophilia in RVO patients should be made. Due to its multifactorial nature, treatment of RVO is still a challenge. In those patients in whom some type of thrombophilia is detected, prophylaxis with LMWH is indicated for situations at risk for venous thrombosis. Moreover, individualized assessment of anticoagulation therapy should be considered in patients with antiphospholipid syndrome or congenital disorders with greater thrombotic potential. In the remaining patients, accounting for the vast majority of RVO cases, it is advisable, from a cardiovascular risk point of view, to prescribe antiplatelet agents, generally aspirin.

**Author contributions: RBS, AD, FM, IC, CK, & ZB:** study conception & design; **RBS, AD, & FM:** material preparation & data collection & analysis; **AD:** writing the first draft; & **CK & ZB:** supervision. All authors have agreed with the results and conclusions.

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**Declaration of interest:** No conflict of interest is declared by the authors.

**Data sharing statement:** Data supporting the findings and conclusions are available upon request from the corresponding author.

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