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ORIGINAL ARTICLE

Long-term mortality after retinal artery occlusion – a single centre study

Joanna Roskal-Wałek[1,2,A-D], Jerzy Mackiewicz[3,E-F], Paweł Wałek[4,2,A-D] ✉, Jacek Sidło[1,B], Michał Biskup[1,E], Beata Wożakowska-Kapłon[4,2,E-F], Dominik Odrobina[5,2,E-F]

[1] *Department of Ophthalmology, Regional Hospital, Kielce, Poland*
[2] *Collegium Medicum, Jan Kochanowski University, Kielce, Poland*
[3] *Department of Vitreoretinal Surgery, Medical University, Lublin, Poland*
[4] *1st Clinic of Cardiology and Electrotherapy, Swietokrzyskie Cardiology Centre, Kielce, Poland*
[5] *Ophthalmology Clinic Boni Fratres Lodziensis, Łódź, Poland*
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

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Abstract

Introduction and Objective. Retinal artery occlusion (RAO) is an ophthalmic and systemic emergency requiring urgent diagnosis and treatment. Data regarding mortality in this group, especially in the European population, are modest. The aim of this study is to assess all-cause mortality in post-RAO patients.

Materials and method. This is a retrospective, single-centre study involving 198 patients following RAO diagnosed in 2004–2020. The control group included 198 patients after cataract surgery matched for gender and age, with the date of cataract surgery corresponding to the date of the RAO.

Results. The average follow-up of the study population was 6.32±2.15 years. Post-RAO patients had significantly higher risk of all-cause mortality (Log-rank test p=0.001), also when stratified for ages below 75 years (Log-rank test p=0.016) and those aged 75 and over (Log-rank test p=0.001). In the group of patients without cardiovascular events before RAO/cataract surgery, post-RAO patients were also at higher risk of all-cause mortality (Log-rank test p=0.011), but when stratified according to age, those observations were borderline significant (Log-rank test p=0.083 for a group of patients aged less than 75 years, and p=0.051 for patients aged 75 and over). Cox analysis showed that in the group of post-RAO patients, the main risk factors for all-cause mortality were age (HR 1.07, 95%CI 1.04–1.1; p<0.001), ischemic heart disease (HR 1.72; 95%CI 1.08–2.72; p=0.022), and permanent atrial fibrillation (HR 2.18, 95%CI 1.08–4.38; p=0.029).

Conclusions. Regardless of age and previous cardiovascular events, post-RAO patients are at a higher risk of all-cause mortality than patients without a history of RAO.

Key words

stroke, all-cause mortality, retinal artery occlusion, myocardial infarction

INTRODUCTION

Retinal artery occlusion (RAO) is an ophthalmic and systemic emergency requiring urgent diagnosis and treatment [1]. Despite over 150 years of research, there are no effective, evidence-based treatments for this condition, although our knowledge about these episodes has increased significantly [2]. Currently, it is known that they occur mainly in the elderly population and often constitute a symptom of cardiovascular disease [1–4]. Patients with RAO are a group in which hypertension, hyperlipidaemia, smoking, and diabetes were diagnosed significantly more frequently than in the control groups [5, 6]. Recently, it has also been indicated that patients with RAO often have undiagnosed atrial fibrillation (AF) [7]. Cardiovascular diseases, often numerous and undiagnosed in patients with RAO, increase the mortality risk in the group [1, 3]. It has also been shown that patients with RAO have a shortened life expectancy [8]. Patients with RAO have a significantly higher risk of stroke, myocardial infarction (MI) or death than the control groups [6, 9–12]. Due to its similarities in aetiology and cardiovascular risk factors, RAO is recognized as the equivalent of acute cerebral ischaemia [1].

It is recommended that patients with RAO undergo urgent diagnostics, similar to those dedicated to patients with ischemic stroke (IS), in order to determine the aetiology of RAO [1]. Increasing attention is being paid to appropriate diagnostic management and secondary prevention aimed at reducing the risk of subsequent thromboembolic episodes and mortality in this group of patients [1, 2, 4]. The results of previous studies show that the patients with RAO, so far, have only rarely been subjected to appropriate diagnostic management [13, 14]. Data on the mortality of patients with RAO are modest, some studies were performed decades ago, not all of the available studies present consistent results, moreover there are few studies with a large study group, long follow-up period or a control group [8, 12, 15–29]. The aim of this study was to assess long-term mortality after RAO in the European population, and to identify risk factors for death in this group of patients.

MATERIALS AND METHOD

The protocol for the retrospective study was approved by a Bioethics Committee, and included 198 patients with RAO

✉ Address for correspondence: Paweł Wałek, 1st Clinic of Cardiology and Electrotherapy, Swietokrzyskie Cardiology Centre, Kielce, Poland
E-mail: pawel.walek@o2.pl

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hospitalized in the Department of Ophthalmology between 2004–2020 due to RAO confirmed by an ophthalmological examination. All-cause mortality data were obtained from the Polish National Health Fund. The inclusion of patients with RAO has been described previously [28]. The control group included patients after cataract surgery performed at the Department of Ophthalmology. The controls were matched to the RAO group according to the date of the cataract surgery that corresponded to the RAO event, as well as according to age and gender. Patients included in the control group were randomly selected from 18,200 patients subjected to cataract surgery between 2004–2020 who matched the described requirements. Finally, 198 patients with RAO confirmed by an ophthalmological examination and 198 patients after cataract surgery hospitalized between 2004–2020 were enrolled in the study. Each patient after cataract surgery performed at our centre was examined for the presence of retinal vascular occlusive disorders (RVOD). A thorough ophthalmological examination of patients after cataract surgery showed that one patient randomized to the control group after the assessment of additional tests, was excluded from the control group due to diagnosed branch retinal artery occlusion (BRAO). Each patient was followed for up to 17 years from the time of diagnosis of RAO or cataract surgery. Data on concomitant diseases were obtained from the medical records due to the hospitalization for RAO or cataract surgery. Patients were classified as having hypercholesterolaemia if they were diagnosed with hypercholesterolaemia before admission, had elevated total cholesterol (>190 mg/dL) or low-density lipoprotein (LDL) cholesterol on admission, or were using lipid-lowering medications at the time of RAO. Patients were classified as having ischemic heart disease if they had a history of MI, had undergone percutaneous coronary intervention or coronary artery bypass grafting, or had been diagnosed with ischemic heart disease by a cardiologist. The profile of the drugs taken represents the medical therapy of patients at the time of admission to the hospital for RAO. At the time of discharge after an episode of RAO, if the patient had not previously taken acetylsalicylic acid or an oral anticoagulant for AF, the patient received acetylsalicylic acid or oral anticoagulant, as indicated.

The date of all-cause mortality was determined on the basis of the data of the National Health Fund.

Statistical Analysis. The demographic and clinical characteristics of the RAO patients were compared with those of the control group using the Student's t-test for normally distributed variables, and the Mann-Whitney or Chi-square test for normally distributed variables. The RAO group baseline characteristics were defined at the time of the RAO episode. Times to event are presented as medians and interquartile ranges (IQR), after which they were compared using the Mann-Whitney U test. The all-cause mortality-free rate were estimated using the Kaplan-Meier method, and log-rank tests were used to describe and compare the curves of patients with RAO and the control group.

Kaplan-Meier analysis with log-rank test was performed for the entire study population and separately for patients aged less than 75 years or those aged 75 years or more, as well for patients who had no history of cardiovascular events such as IS or MI prior to RAO, i.e. patients who did not receive secondary prevention of recurrence of cardiovascular events.

Cox proportional hazards regression analysis was conducted to determine the relationship between cardiovascular risk factors and all-cause mortality in the RAO group.

Statistical significance was set at $p<0.05$. Statistical analyses were performed with STATISTICA 13.3 software (TIBCO Software Inc., Tulsa, OK, USA).

RESULTS

The characteristics of the study group and the control group are presented in Table 1. Comparative analysis showed no differences in age and gender, as assumed by the study methodology. Patients after RAO were more burdened with diseases and cardiovascular risk factors, more often diagnosed with hypertension (82.3 vs 62.1%; $p<0.001$), hypercholesterolaemia (63.1 vs 21.7%; $p<0.001$), ischemic heart disease (41.9 vs 32.3%; $p=0.048$), post-MI status (21.2 vs 9.1%; $p=0.001$), heart failure (16.7 vs 9.1%; $p=0.024$), status post IS or transient cerebral ischemia (12.1 vs 3.5%; $p=0.001$), and AF (14.7 vs 7.6%; $p=0.025$), compared to the control group (Tab. 1). Patients after RAO smoked more often (24.2 vs 11.1%; $p=0.001$), and used acetylsalicylic acid (17.2 vs 10.1%; $p=0.04$) and oral anti-coagulants (13.1 vs 6.1%; $p=0.017$) more often, compared to the group control. Patients after RAO died more often (36.6 vs 23.7%; $p=0.006$), but there was no

Table 1. Study group characteristics

Variables	RAO population n = 198	Control group n = 198	p-Value
Gender (female), n (%)	75(37.9)	74(37.4)	0.917
Age, years (SD)	70.3(11.4)	70.2(11.0)	0.901
Age < 50 years, n (%)	10(5.1)	10(5.1)	
Age 50–59 years, n (%)	20(10.1)	21(10.6)	
Age 60–69 years, n (%)	57(28.8)	56(28.3)	0.999
Age 70–79 years, n (%)	69(34.9)	71(35.9)	
Age ≥ 80 years, n (%)	42(21.2)	40(20.2)	
Age <75 years, n (%)	120(60.6)	120(60.0)	0.902
Hypertension, n (%)	163(82.3)	123(62.1)	<0.001
Hypercholesterolaemia, n (%)	125(63.1)	43(21.7)	<0.001
Ischemic heart disease, n (%)	83(41.9)	64(32.3)	0.048
Post-MI, n (%)	42(21.2)	18(9.1)	0.001
Heart failure, n (%)	33(16.7)	18(9.1)	0.024
Post stroke/TIA, n (%)	24(12.1)	7(3.5)	0.001
Post haemorrhagic stroke, n (%)	3(1.5)	0(0.0)	0.082
AF, n (%)	29(14.7)	15(7.6)	0.025
Permanent AF, n (%)	14(7.1)	11(5.6)	0.535
Paroxysmal AF, n (%)	15(7.6)	4(2.0)	0.010
Diabetes, n (%)	37(18.8)	51(25.8)	0.096
Smoking, n (%)	48(24.2)	22(11.1)	0.001
ASA, n (%)	34(17.2)	20(10.1)	0.04
OAK, n (%)	26(13.1)	12(6.1)	0.017
VKA, n (%)	22(11.1)	6(3.0)	0.002
NOAC, n (%)	5(2.5)	5(2.5)	1.000
Death, n (%)	72(36.6)	47(23.7)	0.006
Median time to death, months (IQR)	49.1(68.9)	65.6(58.7)	0.215

AF – atrial fibrillation; ASA – acetylsalicylic acid; IQR – interquartile range; MI – myocardial infarction; NOAC – non-vitamin K antagonist oral anticoagulants; OAK – oral anti-coagulant; SD – standard deviation; TIA – transient ischaemic attack; VKA – vitamin K antagonists

difference in the median time to death (49.1 vs 65.6 months; p=0.215) compared to the control group.

The average follow-up of the study population was 6.32±2.15 years.

Figure 1A shows the results of the Kaplan-Meier curves for the RAO group and the control group. The Kaplan-Meier analysis of the occurrence of all-cause mortality in the RAO group and the control group showed that patients after RAO were at a statistically significantly higher risk of all-cause mortality compared to the control group (log-rank test p=0.001).

Due to the elderly age of the study population, a Kaplan-Meier analysis was performed with stratification into two groups for age at the time of the RAO event/cataract surgery. Both the population under 75 years of age (log-rank test p=0.016) and the population over or at 75 years (log-rank test p=0.001) after RAO, were at higher risk of all-cause mortality than the control group (Fig. 1B and 1C).

Kaplan-Meier analysis for the group of patients without cardiovascular events before RAO showed that patients after RAO were more likely to experience all-cause mortality compared to the control group (log-rank test p=0.011), but when stratified according to age groups these findings were borderline statistically significant for patients under 75 years of age (Log-rank test p=0.083), and for patients 75 years or older (Log-rank test p=0.051) (Fig. 2A-C).

Cox analysis showed that in the group of post-RAO patients the main risk factors for all-cause mortality were age (HR 1.07; 95%CI 1.04–1.1; p<0.001), ischemic heart disease (HR 1.72; 95%CI 1.08–2.72; p=0.022), and permanent AF (HR 2.18, 95%CI 1.08–4.38; p=0.029) (Tab. 2).

Table 2. Risk factors for all-cause mortality identified by univariate Cox analysis in RAO patients

	Univariate Cox		
	HR	95%CI	p-Value
Age, years	1.07	1.04–1.10	<0.001
Age ≥75 years	2.68	1.66–4.29	<0.001
Gender (female)	0.98	0.61–1.57	0.937
Ischaemic heart disease	1.72	1.08–2.72	0.022
Permanent AF	2.18	1.08–4.38	0.029
Paroxysmal AF	0.72	0.29–1.79	0.485
Heart Failure	1.15	0.63–2.11	0.639
Myocardial infarction before RAO	1.2	0.67–2.16	0.536
Smoking	0.91	0.52–1.58	0.727
Diabetes mellitus	1.2	0.67–2.15	0.538
Ischaemic stroke/TIA before RAO	0.95	0.47–1.91	0.886
Hypertension	1.47	0.77–2.79	0.243
Hypercholesterolaemia	0.88	0.56–1.41	0.607

AF – atrial fibrillation; RAO – retinal artery occlusion; TIA – transient ischemic attack

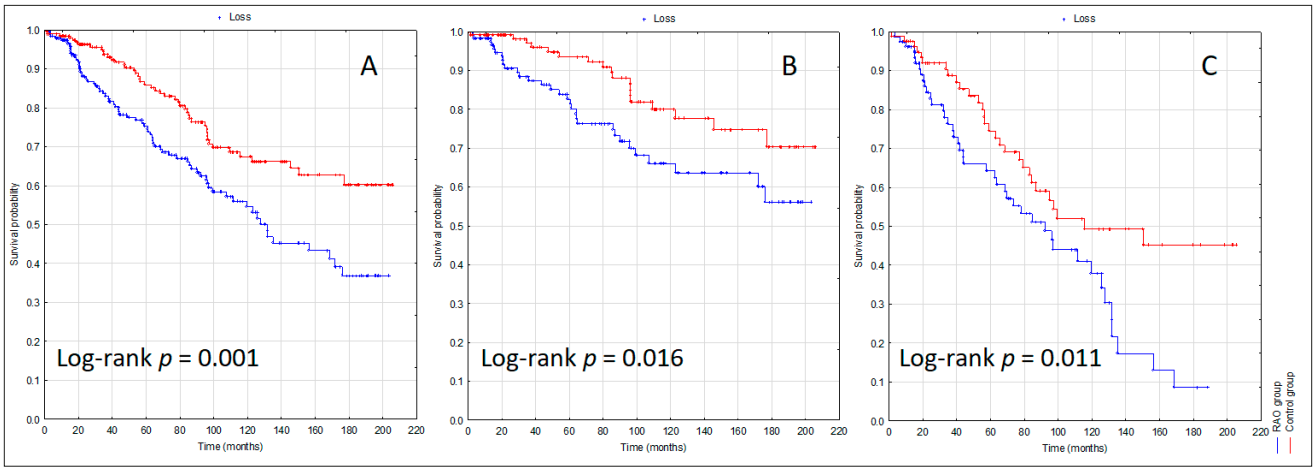

Figure 1. Kaplan–Meier survival probability curves for all-cause mortality for the whole study population (A), patients younger than 75 years old (B), and patients at 75 years or older (RAO, blue line; control group, red line).

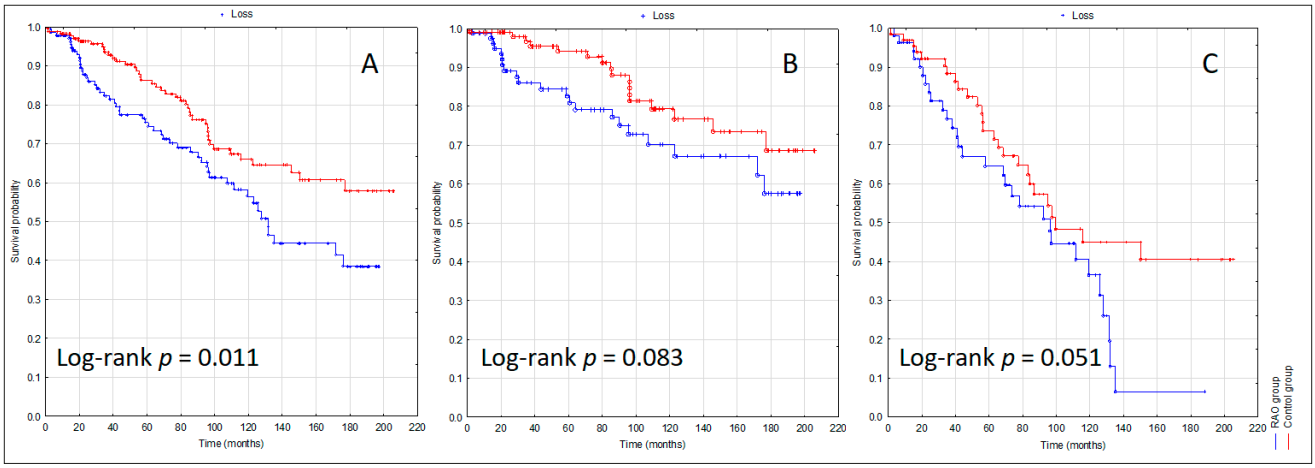

Figure 2. Kaplan–Meier survival probability curves for all-cause mortality for a sub-population without cardiovascular events before RAO for the whole study population (A), patients younger than 75 years old (B), and patients at 75 years or older.
RAO – blue line; control group – red line.

DISCUSSION

The study found that patients with RAO had statistically significantly higher risk of all-cause mortality compared to the control group who did not experience RAO. This finding applied to both patient groups: under 75 years and those aged 75 and over. A poorer prognosis in the group of RAO patients in terms of all-cause mortality was also applicable to patients without previously diagnosed cardiovascular events, such as MI or IS, compared to patients in the control group also without cardiovascular events, i.e. patients who did not receive secondary prevention for cardiovascular events. Among the studied variables, risk factors for all-cause mortality were identified in patients after RAO, which were age, ischemic heart disease, and permanent AF.

The assessments of mortality in patients with RAO have been undertaken in several studies [8, 12, 15–29], some of which date back over forty years [8, 16, 17], and show that patients with RAO had a shortened life expectancy [8, 16, 17]. However, the study by De Potter et al. concluded that although the survival rate of 151 RAO patients was lower than that of the age- and gender-matched control group, there was no statistically significant difference in the survival rate between RAO patients and control group (26% vs 21%; P=0.29). The follow-up lasted 9.7 years [20]. In the systematic review by Woo et al., aimed at assessing the relationship between RAO and retinal vein occlusion (RVO) with mortality, stroke, and MI, the analysis included papers regarding this issue published between 1992–2015. The review did not include any study that would assess mortality in patients with RAO [30]. When considering mortality in patients with RAO, the study by Wang et al. in particular must be mentioned. Pooled data analyses from two older populations show that the presence of retinal embolism predicts a modestly increased risk of long-term, all-cause mortality, independent of age, gender, and vascular risk factors [25].

Most studies included patients with RAO [21, 22, 26–29], some studies only included patients with central retinal artery occlusion (CRAO) [23, 24]; the studies also differed in the duration of follow-up and the size of the groups evaluated, and only few studies included a control group [21–24, 26–29]. In the study by Mir et al., in-hospital mortality in CRAO patients was 1.3% [24]. In the study by Suri et al. 308 patients (2.1%) out of 14,527 patients with RAO died within six months from RAO [27]. Lavin et al., assessed the death risk within 24 months after CRAO. Of the 103 patients enrolled in the study, 28 were lost to follow-up within 90 days after CRAO. Of the remaining 75 subjects, six (8%) died [23]. This is a very high result in such a short period of time, but this study was performed in the so-called 'stroke belt' of the USA, where there is a higher burden of stroke risk factors and a higher percentage of strokes identified, which may have had a major impact on the results obtained. In this study, as many as 33% of the patients with RAO had a hypertensive crisis [23].

A recent study by Vestergaard et al. concerning RAO patients among the European population [12] was based on the national health registry, and included the entire population of Denmark between 2000–2018. All patients with RAO were identified and the risk of stroke, MI or death in the periods since RAO were compared with those of the Danish population. All-cause deaths occurred in 6.06% of RAO patients within the first year after RAO. As in the current study, the occurrence of RAO was associated with an increased risk of death compared to the control group. In Vestergaard et al. study, the risk of death after RAO persisted for more than one year, but was the highest at 14–90 days after RAO, with adjusted RRs of 1.64 (95% CI, 1.28–189) [12]. In the current study, the control group was matched for age and gender only, while in the study by Vestergaard et al., the following comorbidities were considered as potential confounders: diabetes, hypertension, heart failure, chronic kidney disease, cancer, ischemic heart disease, stroke, and atrial fibrillation, which significantly increased the significance of the obtained results [12].

The European population was also included in a prospective study performed over 30 years ago by Hankey et al. [15], but which unfortunately did not include a control group. A total of 99 patients with RAO were included in the study, and during the follow-up period which lasted, on average, 4.2 years, 29 deaths (29.29%) were recorded [15]. In the current study, there was a longer observation time, with an average follow-up of 6.32±2.15 years and 72 deaths among 198 subjects recorded (36.6%), which may be due to the longer follow-up. Despite the many years that have passed since the study by Hankey et al., the comparable percentage of cardiovascular risk factors between the current study and that of Hankey et al. attracts attention [15]. The coexisting cardiovascular risk factors in the current study, i.e. arterial hypertension, hypercholesterolaemia, ischemic heart disease, smoking, heart failure, and paroxysmal AF, occurred statistically significantly more often than in the control group. In terms of the prevalence of the above-mentioned diseases, the results obtained are also similar to other previously published studies evaluating cardiovascular risk factors in patients with RAO [3, 6, 15, 24, 27].

Nevertheless, there are some inconsistencies. In the current study, diabetes was not statistically significantly more frequent in RAO patients, and the percentage share of diabetes in RAO patients was also lower compared to other studies [5, 6, 22, 24–27, 29]. Hypertension and hypercholesterolaemia, both in the currrent and other studies, were among the leading cardiovascular risk factors [6, 15, 24, 27]. Noteworthy was the significantly lower prevalence of hypertension and ischemic heart disease in the study by Vestergaard et al. [12], which also applies to the European population, both in comparison to the current and other studies [3, 5, 6, 9, 10, 15, 18, 24, 27, 28, 29].

In a recently published study, Hwang et al. assessed mortality in RAO patients in a South Korean population [29]. The authors used claims data from 2002–2018 in Korea, and found 51,326 RAO patients among whom they identified 7,107 deaths. This study was similar to the current study in terms of the data collecting period, where death was significantly higher in patients with RAO compared with the control group [29]. However, the percentage of deaths in the current study was definitely higher (36.6%vs13.84%). The difference in the incidence rate of death between the studies may result from the fact that patients in the current study were older, with most of them having cardiovascular disease. There are visible significant discrepancies in the frequency of diagnosed diseases, such as hypertension, dyslipidaemia, ischemic heart disease or AF, which were more often diagnosed in the current study, contrary to diabetes mellitus where the incidence was higher in the study Hwang et al. In this case, ethnic differences may also be significant [29].

It is well known that stroke is the leading cause of death worldwide [31]. Undoubtedly, it should be remembered that the different subtypes of stroke differ in terms of the related risk of death, as in this context the risk in patients with RAO, which is compared to minor strokes, is more interesting [1, 32, 33]. Mortality in patients with a minor stroke is lower than mortality observed in stroke patients taken as a whole, because they are not affected by deaths caused by the extent of ischemic stroke or complications related to immobilization [32]. The study by Schorr et al. showed a statistically significant difference in mortality rates between patients with RAO and those with ischemic stroke. In that study, a minor likelihood of dying affected 60.1% of patients with RAO and 29.8% of patients with stroke, the extreme likelihood of dying affected 0.4% of patients with RAO and 8.5% of patients with ischemic stroke [26]. However, there are no studies comparing the mortality of patients with RAO to patients with a minor stroke.

In a study by Prencipe et al. evaluating the long-term prognosis after a minor stroke, the 10-year mortality rate was 32% for stroke patients and 17% for the age- and gender-matched general population. This is similar to the results obtained in the current study, with all-cause mortality for RAO at 36.6% and 23.7% for the control group [32].

In minor ischemic strokes, age, minor disability, MI, non-valvular AF, and hypercholesterolaemia increased the risk of death [32]. In the study by Hankey et al., the prognostic factors associated with an increased risk of death were increasing age, peripheral vascular disease, cardiomegaly, and carotid bruit [15]. In the current study, the factors were age, ischemic heart disease, and permanent AF.

It is very important that after RAO, in comparison to the control groups, a statistically significantly higher incidence of ischemic episodes, such as strokes and MI, was reported, where the risk of stroke was highest in the first weeks after RAO [9, 11, 12]. Studies evaluating the incidence of stroke in patients with RAO based on MRI show that most lesions are small and clinically silent [34], which would confirm previous reports that heart disease, and not the stroke itself after RAO, was the main cause of death after RAO [15–19]. Nevertheless, it should be remembered that the presence of even small cerebrovascular lesions is associated with an increased risk of subsequent stroke and mortality [35, 36].

In the study by Hankey et al., during the follow-up there were 29 deaths, 21 from vascular causes and eight from non-vascular or unknown causes, 10 patients had a first-ever stroke, while 19 patients had a coronary event. A coronary event accounted for more than half (59%) of the deaths, whereas stroke was the cause of only one death (3%). Over the first five years after retinal infarction, the actuarial average absolute risk of death was 8% per year [15].

In the study by Laczynski et al., which included 221 patients with RAO, only five patients (2.3%) experienced a stroke, while four of the five strokes occurred during the RAO, and were minor in severity. Of the 221 RAO patients enrolled in the study, 12 (5.4%) died during the mean follow-up period of 24.5 months, two due to MI, while in the remaining cases the cause of death was unknown [22].

In the study by Dunlap et al., 130 patients with CRAO, BRAO, and Hollenhorst plaque were evaluated. The follow-up data ranged from one to 49 months (median – 22 months). A total of five people died with none of the deaths being related to stroke. A total of two patients died of heart disease: one of post-MI and the other due to congestive heart failure. Two patients died of cancer, while one patient died due to complications following a hip fracture. Stroke-free survival and overall survival were 94%, equivalent to three years [18].

Plaffenbach and Hollenhorst noted that 15% of patients with ophthalmologically visible cholesterol embolism died within the first year, 29% within the first three years, and 54% within the first seven years. Most deaths were related to coronary artery disease [17].

Contrary to the results of the above studies, Wang et al. did not find a significant association between retinal embolism and cardiovascular mortality. In the study by Wang et al., after adjusting for age, gender, body mass index, hypertension, diabetes, current smoking status, total cholesterol, HDL cholesterol, and study site, stroke-related mortality doubled in participants with retinal emboli (Model 1 HR, 2.5; CI, 1.4 to 4.4); however, there was no statistically significant increase in cardiovascular mortality in this group (Model 1 HR, 1.3; CI, 0.9 to 1.8) [25]. In the study by Hwang et al., the leading causes of death among patients with RAO were diseases of the circulatory system, including acute MI (18.6%) and cerebral infarction (15.9%). By comparison, in the general population of this study, the most common cause of death involved neoplasms [29].

In the current study, no cause of death was determined, but data on the frequency of strokes and heart attacks after RAO were provided in previous publications by the authors [28]. Patients with RAO under 75 years of age had a statistically significantly higher risk of stroke and all-cause mortality compared to the control group, while similar findings were not found for patients over 75 years of age [28]. In the present study with a longer follow-up period, all-cause mortality was statistically significantly more frequent, both in the group of patients both below and above 75 years of age. In this study, it was found that RAO patients were statistically significantly more likely to experience MI and stroke before an episode of RAO, which also implied a statistically significantly more frequent use of anti-platelets in the entire RAO group and anti-coagulants in the RAO group with AF. However, despite this treatment, the patients still developed an episode of RAO. The observations were not surprising given the numerous cardiovascular risk factors present in patients with RAO. This is an interesting observation in the context of previous reports, which indicate the lack of the protective effect of aspirin on the risk of subsequent strokes after RAO [12, 15, 37].

In the study by Vestergaard et al., treatment with aspirin did not change the risk of stroke, MI, or death in the first year after RAO, but after one year of the treatment with aspirin it was associated with a reduction in the risk of both strokes (adjusted RR, 0.80; 95% CI, 0.68–0.94; p=0.0058) and death (adjusted RR, 0.86; 95% CI, 0.79–0.93; p<0.001). Clopidogrel was associated with a reduced risk of death after one year, with an adjusted RR of 0.84 (95% CI, 0.74–0.95; p=0.0068). Anti-coagulant treatment was associated with a reduction in the risk of stroke at all time intervals, and of MI and death at 90 and 365 days, respectively [12]. Similarly, in the study by Hankey et al., the treatment with aspirin and anti-coagulation did not have a significant effect on the risk of subsequent stroke, but the evaluated group was small [15]. A study by Kang et al. also failed to demonstrate the benefit of aspirin in reducing the risk of stroke after RAO [37].

Only a few studies compare mortality between CRAO and BRAO patients [20, 29, 38]. In the study by De Potter and Zografos only BRAO was associated with a significant lower life expectancy [20]. Contrary to the study by Hwang et al. the mortality rate was higher in CRAO than in the non-central RAO group [29]. In their previous study, the authors of the presented study found no statistically significant differences in all-cause mortality between patients with CRAO and BRAO [38].

Strengths of the Study. Only patients with diagnosed RAO confirmed by research team were included in the study, which excluded misdiagnoses. The study population was ethnically homogeneous as only European patients were included. This was important in the light of reported differences in the risk of ischemic stroke and RAO between ethnic groups. The follow-up lasted 17 years, the average follow-up of the study population was 6.32±2.15 years, which is one of the longest follow-up periods among studies evaluating the mortality of patients after RAO, compared to the control group. Finally, a control group was randomly selected and matched for gender, age, and year of RAO event/cataract surgery. Each control patient was assessed for ocular vascular occlusion disorders, and all patients suspected of having RAO were excluded from the control group.

Limitations of the Study. Due to the lack of detailed information on the actual cause of death, all-cause mortality was used in the analysis. Due to the reported differences in the all-cause mortality and RAO across ethnic groups, the results obtained should not be generalized to other populations. Although this study presents one of the longest reported follow-up periods in patients after RAO, this group is relatively small because RAO is a relatively rare disease, diagnosed, and treated in ophthalmology departments. Moreover, it is a single-centre study. This may have affected the borderline statistical significance in the analysis of some variables. Due to the small sample size and the burden of cardiovascular diseases, it is difficult to match the control group in terms of these parameters, which results in matching the control group only in terms of age, gender, and the year of RAO occurrence. The correction for these variables only excludes the assessment of the risk of cardiovascular events, which would be affected only by the RAO event. Due to the cardiovascular burden in the RAO group, it can be assumed that the more frequent deaths in this group result from the overall cardiovascular risk resulting from these diseases, and not only from a previous episode of RAO.

Patients in the control group did not undergo a Doppler ultrasound of the carotid arteries; therefore, these parameters could not be compared between patients after RAO and the control group, even though one of the main sources of embolic material in RAO patients is atherosclerotic plaque in the carotid arteries. No tests were performed for hypercoagulation statuses.

CONCLUSIONS

Patients with RAO were more likely to have cardiovascular diseases and risk factors than the control group matched for gender, age, and year of RAO event/cataract surgery. Regardless of their age and previous cardiovascular events, post-RAO patients were at higher risk of all-cause mortality than patients without a history of RAO. The main risk factors for all-cause mortality in the group after RAO were age, ischemic heart disease, and permanent AF. Due to the higher risk of all-cause mortality, these patients should be diagnosed as soon as possible for RAO aetiology and related cardiovascular diseases in order to introduce treatment that may affect their long-term prognosis. Due to the fact that cardiovascular events are the main cause of death globally, it is warranted to look for ways to improve the prognosis in post-RAO patients. A multi-centre randomized trial should be designed to evaluate the effectiveness of antiplatelet, antithrombotic, and lipid-lowering treatments in patients with RAO.

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REFERENCES

1. Biousse V, Nahab F, Newman NJ. Management of Acute Retinal Ischemia: Follow the Guidelines! Ophthalmology. 2018;125(10):1597–1607. doi:10.1016/j.ophtha.2018.03.054
2. Mac Grory B, Schrag M, Biousse V, et al. Management of Central Retinal Artery Occlusion: A Scientific Statement From the American Heart Association Stroke. 2021;52(6):e282–e294. doi:10.1161/STR.0000000000000366
3. Callizo J, Feltgen N, Pantenburg S, et al. Cardiovascular Risk Factors in Central Retinal Artery Occlusion: Results of a Prospective and Standardized Medical Examination. Ophthalmology. 2015;122(9):1881–1888. doi:10.1016/j.ophtha.2015.05.044
4. Feltgen N, Liman J, Schultheiss M, et al. Retinaler nichtarteriitischer Zentralarterienverschluss als Marker für das generalisierte vaskuläre Risiko [Nonaretritic central retinal artery occlusion as marker for the generalized vascular risk]. Ophthalmologe. 2021;118(11):1093–1098. doi:10.1007/s00347-021-01466-6
5. Hayreh SS, Podhajsky PA, Zimmerman MB. Retinal artery occlusion: associated systemic and ophthalmic abnormalities. Ophthalmology. 2009;116(10):1928–1936. doi:10.1016/j.ophtha.2009.03.006
6. Rim TH, Han J, Choi YS, et al. Retinal Artery Occlusion and the Risk of Stroke Development: Twelve-Year Nationwide Cohort Study. Stroke. 2016;47(2):376–382. doi:10.1161/STROKEAHA.115.010828
7. Vonderlin N, Kortuem K, Siebermair J, et al. Central retinal artery occlusion as a first sign of atrial fibrillation: A 3-year retrospective single-centre analysis. Clin Cardiol. 2021;44(12):1654–1661. doi:10.1002/clc.23673
8. Lorentzen SE. Occlusion of the central retinal artery. A follow-up. Acta Ophthalmol (Copenh). 1969;47(3):690–703. doi:10.1111/j.1755-3768.1969.tb08157.x
9. Chang YS, Jan RL, Weng SF, et al. Retinal artery occlusion and the 3-year risk of stroke in Taiwan: a nationwide population-based study. Am J Ophthalmol. 2012;154(4):645–652.e1. doi:10.1016/j.ajo.2012.03.046
10. Chang YS, Chu CC, Weng SF, et al. The risk of acute coronary syndrome after retinal artery occlusion: a population-based cohort study. Br J Ophthalmol. 2015;99(2):227–231. doi:10.1136/bjophthalmol-2014-305451
11. French DD, Margo CE, Greenberg PB. Ischemic Stroke Risk in Medicare Beneficiaries with Central Retinal Artery Occlusion: A Retrospective Cohort Study. Ophthalmol Ther. 2018;7(1):125–131. doi:10.1007/s40123-018-0126-x
12. Vestergaard N, Torp-Pedersen C, Vorum H, et al. Risk of Stroke, Myocardial Infarction, and Death Among Patients With Retinal Artery Occlusion and the Effect of Antithrombotic Treatment. Transl Vis Sci Technol. 2021;10(11):2. doi:10.1167/tvst.10.11.2
13. Meer E, Scoles D, Hua P, et al. Recent Practice Patterns in Acute Retinal Artery Occlusions in the United States. Ophthalmic Epidemiol. 2022;29(6):696–702. doi:10.1080/09286586.2021.2020297

14. Hoyer C, Kahlert C, Güney R, et al. Central retinal artery occlusion as a neuro-ophthalmological emergency: the need to raise public awareness. Eur J Neurol. 2021;28(6):2111–2114. doi:10.1111/ene.14735
15. Hankey GJ, Slattery JM, Warlow CP. Prognosis and prognostic factors of retinal infarction: a prospective cohort study. BMJ. 1991;302(6775):499–504. doi:10.1136/bmj.302.6775.499
16. Savino PJ, Glaser JS, Cassady J. Retinal stroke. Is the patient at risk? Arch Ophthalmol. 1977;95(7):1185–1189. doi:10.1001/archopht.1977.04450070083005
17. Pfaffenbach DD, Hollenhorst RW. Morbidity and survivorship of patients with embolic cholesterol crystals in the ocular fundus. Am J Ophthalmol. 1973;75(1):66–72. doi:10.1016/0002-9394(73)90653-3
18. Dunlap AB, Kosmorsky GS, Kashyap VS. The fate of patients with retinal artery occlusion and Hollenhorst plaque. J Vasc Surg. 2007;46(6):1125–1129. doi:10.1016/j.jvs.2007.07.054
19. Bruno A, Jones WL, Austin JK, et al. Vascular outcome in men with asymptomatic retinal cholesterol emboli. A cohort study. Ann Intern Med. 1995;122(4):249–253. doi:10.7326/0003-4819-122-4-199502150-00002
20. De Potter P, Zografos L. Survival prognosis of patients with retinal artery occlusion and associated carotid artery disease. Graefes Arch Clin Exp Ophthalmol. 1993;231(4):212–216. doi:10.1007/BF00918843
21. Hong JH, Sohn SI, Kwak J, et al. Retinal artery occlusion and associated recurrent vascular risk with underlying etiologies. PLoS One. 2017;12(6):e0177663. doi:10.1371/journal.pone.0177663
22. Laczynski DJ, Gallop J, Lyden SP, et al. Retinal artery occlusion does not portend an increased risk of stroke. J Vasc Surg. 2020;72(1):198–203. doi:10.1016/j.jvs.2019.08.279
23. Lavin P, Patrylo M, Hollar M, et al. Stroke Risk and Risk Factors in Patients With Central Retinal Artery Occlusion. Am J Ophthalmol. 2018;196:96–100. doi:10.1016/j.ajo.2018.08.027
24. Mir TA, Arham AZ, Fang W, et al. Acute Vascular Ischemic Events in Patients With Central Retinal Artery Occlusion in the United States: A Nationwide Study 2003–2014. Am J Ophthalmol. 2019;200:179–186. doi:10.1016/j.ajo.2019.01.009
25. Wang JJ, Cugati S, Knudtson MD, et al. Retinal arteriolar emboli and long-term mortality: pooled data analysis from two older populations. Stroke. 2006;37(7):1833–1836. doi:10.1161/01.STR.0000226929.23297.75
26. Schorr EM, Rossi KC, Stein LK, et al. Characteristics and Outcomes of Retinal Artery Occlusion: Nationally Representative Data. Stroke. 2020;51(3):800–807. doi:10.1161/STROKEAHA.119.027034
27. Suri K, Majmundar M, Kumar A, et al. Outcomes and Readmission in Patients With Retinal Artery Occlusion (from the Nationwide Readmission Database). Am J Cardiol. 2022;183:105–108. doi:10.1016/j.amjcard.2022.07.040
28. Roskal-Wałek J, Wałek P, Biskup M, et al. Retinal Artery Occlusion and Its Impact on the Incidence of Stroke, Myocardial Infarction, and All-Cause Mortality during 12-Year Follow-Up. J Clin Med. 2022;11(14):4076. Published 2022 Jul 14. doi:10.3390/jcm11144076
29. Hwang DDJ, Lee KE, Kim Y, et al. Incidence of Retinal Artery Occlusion and Related Mortality in Korea, 2005 to 2018. JAMA Network Open, 2023;6(3):e233068-e233068.
30. Woo SC, Lip GY, Lip PL. Associations of retinal artery occlusion and retinal vein occlusion to mortality, stroke, and myocardial infarction: a systematic review. Eye (Lond). 2016 Aug;30(8):1031–8. doi: 10.1038/eye.2016.111. Epub 2016 Jun 3. PMID: 27256303; PMCID: PMC4985669
31. Gattringer T, Posekany A, Niederkorn K, et al. Predicting Early Mortality of Acute Ischemic Stroke. Stroke. 2019;50(2):349–356. doi:10.1161/STROKEAHA.118.022863
32. Prencipe M, Culasso F, Rasura M, et al. Long-term prognosis after a minor stroke: 10-year mortality and major stroke recurrence rates in a hospital-based cohort. Stroke. 1998;29(1):126–132. doi:10.1161/01.str.29.1.126
33. Roskal-Wałek J, Mackiewicz J, Wałek P, et al. Retinal artery occlusion and its association with stroke –literature review. Medical Studies/Studia Medyczne. 2023;39(1):55–64. doi:10.5114/ms.2023.126296
34. Fallico M, Lotery AJ, Longo A, et al. Risk of acute stroke in patients with retinal artery occlusion: a systematic review and meta-analysis. Eye (Lond). 2020;34(4):683–689. doi:10.1038/s41433-019-0576-y
35. Bokura H, Kobayashi S, Yamaguchi S, et al. Silent brain infarction and subcortical white matter lesions increase the risk of stroke and mortality: a prospective cohort study. J Stroke Cerebrovasc Dis. 2006;15(2):57–63. doi:10.1016/j.jstrokecerebrovasdis.2005.11.001
36. Windham BG, Deere B, Griswold ME, et al. Small Brain Lesions and Incident Stroke and Mortality: A Cohort Study. Ann Intern Med. 2015;163(1):22–31. doi:10.7326/M14-2057
37. Kang EY, Lin YH, Wang NK, et al. Aspirin use in central retinal arterial occlusion to prevent ischaemic stroke: a retrospective cohort study in Taiwan. BMJ Open. 2019;9(2):e025455. doi:10.1136/bmjopen-2018-025455
38. Roskal-Wałek J, Wałek P, Biskup M, et al. Central and Branch Retinal Artery Occlusion-Do They Harbor the Same Risk of Further Ischemic Events? J Clin Med. 2021;10(14):3093. doi:10.3390/jcm10143093