Risk of acute stroke in patients with retinal artery occlusion: a systematic review and meta-analysis

O. AL JARALLAH

Department of Surgery, College of Medicine, Prince Sattam Bin Abdulaziz University, AlKharj, Saudi Arabia

Abstract. – OBJECTIVE: In this systematic review and subsequent meta-analysis, we evaluated studies that showed a relationship between stroke and renal artery occlusion in order to determine the risk of acute stroke in patients with retinal artery occlusion (RAO).

MATERIALS AND METHODS: The guiding principles of PRISMA were followed in this investigation. Using the keywords, 850 similar articles from the years 2004 to 2022 during the initial screening. The remaining research underwent additional screening, and 350 studies were excluded for not meeting our inclusion criteria. In the end, 12 papers were chosen for analysis.

RESULTS: The odd ratios were calculated using a random effect model. Then the I2 test was used to determine heterogeneity. To generate the conclusions, one sizable cohort of French studies was taken from the meta-analysis. Every study found a strong link. In half of the chosen trials, we found a marginal connection between stroke risk and retinal artery obstruction. The remaining research, however, reveals a considerable positive association between the two factors.

CONCLUSIONS: The meta-analysis demonstrated that people with RAO are significantly more likely to get an acute stroke than patients without RAO. In addition, patients with RAO are substantially more likely than those without RAO to develop an acute stroke following an occlusion episode, especially if they are under 75 years old. However, given that only a small number of the studies in our review did not show a clear correlation between the two, we believe more research is required to conclusively link RAO and the prevalence of acute stroke.

Key Words:
Acute cerebral ischemia, Retinal artery occlusion, Stroke, Vision loss.

Introduction

A decrease in blood flow through the central retinal artery to the inner layers of the retina is known as retinal artery occlusion (RAO)[1]. When this happens, the retina may cause an infarct, consistent with an acute ischemic stroke diagnosis. Additionally, the obstruction of branch retinal arteries, which may involve smaller retinal segments, might cause retinal infarction. The extent of tissue involvement depends on the amount of collateral flow *via* the external carotid artery circulation. Ophthalmic artery obstruction can cause infarction of the inner and outer retina, optic nerve head, globe, and ocular tissues. A relative afferent pupillary deficiency, funduscopic evidence of retinal hypoperfusion, and the usual clinical signs of rapid, painless vision loss are used to diagnose RAO. A separate RAO emerges with a better visual prognosis when a cilioretinal artery is present and spared. In addition, 95 percent of RAO patients are classed as non-arteritic, while only 5 percent of cases are arteritic and involve an inflammatory condition such as giant cell arteritis (GCA)[2]. Incidence rates of RAO, adjusted for age and sex, are 1.9 per 100,000 in the United States[3], 1.8 per 100,000 in South Korea[4], and 2.5 per 100,000 in Japan[5]. Men are more likely to experience it than women[4,6]. Asymptomatic branch retinal arterial emboli are far more common in people over the age of 49, with a cumulative 10-year incidence of 2.9%[7]. In comparison, symptomatic branch retinal artery occlusion is just 30% as common as RAO[8]. Patients admitted with central retinal artery occlusion (CRAO) or obstruction of branch retinal arteries are marginally younger than those with cerebral ischemic stroke, according to a comprehensive study based on the National Readmissions Database in the United States (66.8 years *vs.* 70.8 years)[8].

RAO typically manifests as a rapid, painless loss of visual acuity and peripheral vision in one eye. In more than 80% of patients, the first visual acuity is "count fingers" or worse; however, when a cilioretinal artery is present, the visual loss can be close to normal. Visual acuity and color vision impairment are inversely correlated. A relative afferent pupil-

Corresponding Author: Othman Jarallah Al Jarallah, MD; e-mail: Othman.md@hotmail.com

lary deficiency on the ipsilateral side is common in patients (that may not be present if there is contralateral optic neuropathy). The typical funduscopic features include slow segmental blood flow (also known as box carrying) in the attenuated retinal arteries, a cherry red area (due to intact choroidal circulation below the fovea surrounded by pale, ischemic retina), and typically a normal-appearing optic disc. Retinal emboli are rarely seen within the central retinal artery since most of its path is retrobulbar, and they are rarely evident in the branch retinal arteries in patients with RAO. The connection between acute RAO and optic disc edema points to the unusual coexistence of anterior ischemic optic neuropathy (AION) and inner retinal ischemia, which most likely reflects a vasculitis affecting the posterior ciliary arteries. Patients older than 50 with systemic symptoms such as jaw claudication, polymyalgia rheumatic, generalized posterior neck pain, scalp soreness with or without nodules, new-onset headache, or elevated inflammatory markers should be suspected of having arterial RAO[9,10].

Three distinct vascular retinal disorders, including CRAO, branch retinal artery occlusion (BRAO), and temporary monocular visual loss, are included in monocular vision loss (MVL) of ischemic origin (TMVL). The damaged artery size and occlusion length vary between these disorders[11]. While TMVL is equivalent to a transient ischemic attack, RAO and BRAO have been compared to an ischemia cerebral infarction[12]. Additionally, patients with retinal artery occlusion have an increased risk of developing acute cerebral ischemia, with the highest rate occurring within 7 days of diagnosis[13]. What needs to be solved is whether patients with acute retinal artery occlusion need to be referred immediately to the emergency room or stroke unit for a neurologic examination[14].

Hence, through this systematic review and subsequent meta-analysis, we aimed to assess the risk of acute stroke in patients afflicted with RAO by selecting studies that depicted a correlation between the above two ailments.

Materials and Methods

Protocol Employed

This systematic review was conducted following the Cochrane group's Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines and the Orderly Reviews in Health Care: Meta-Examination book[15].

Review Hypotheses

This meta-analysis was conducted to evaluate the previous literature describing the risk of acute stroke in patients with retinal artery occlusion (RAO).

Study Selection

Using the keywords, we found 850 similar articles from 2004 to 2022 during the initial screening. Unfortunately, 350 studies were excluded because they didn't match the criteria for inclusion; the remaining papers underwent extra screening. In addition, two authors reviewed the complete text of the articles in the second stage and discovered duplication and missing data. Finally, 12 publications were chosen for the study's conclusion (Figure 1).

Inclusion Criteria

For full-text screening, articles that included pertinent information for the review's aims covering all age groups, were chosen. In addition, studies that reported randomized/non-randomized studies, systematic reviews containing substantial sample volume, detailed case reports, and validated questionnaire-based were considered for inclusion in our review.

Exclusion Criteria

The breadth of our systematic investigation excluded studies using animal subjects, seminar presentations, academic articles, opinion pieces, or incomplete data. We did not restrict our search based on when the studies were published; rather, we considered any publications that had been published about this topic. The analysis did not include studies that employed placebos. In addition, we skipped all literature reviews and cases published in languages other than English.

Search Strategy

The databases PubMed-MEDLINE, Web of Science, Cochrane, and Scopus were all searched using relevant keywords, reference searches, and citation searches. For example, "Acute cerebral ischemia", "retinal artery occlusion", "stroke", and "vision loss" were the search terms used to search the database.

Data Selection and Coding

Two independent reviewers searched relevant articles using appropriate keywords in various databases and online search tools. The chosen articles were compared, and a third reviewer was brought in if there was a dispute.

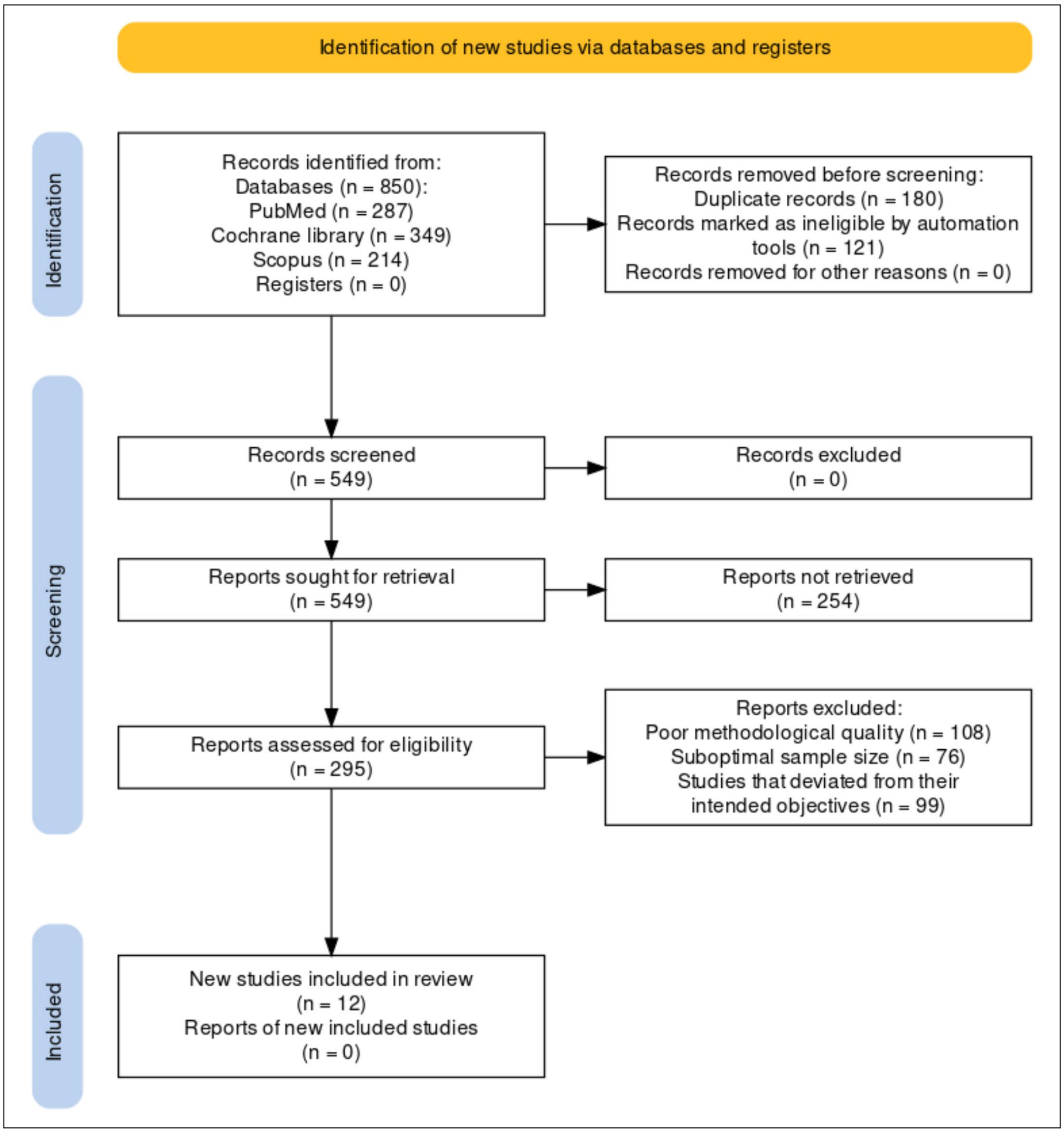

Figure 1. PRISMA checklist representing a selection of articles for this systematic review.

After choosing the articles, the same two reviewers independently extracted the following data: author, year of publication, country, kind of publication, study topic, population demographics (n, age), outcome measure(s), relevant result(s), and conclusion(s). Finally, the data were compared, and any differences were discussed with a third reviewer.

Risk of Bias Assessment

The JBI systematic review appraisal tool[16] was used for assessing the risk of bias in our systematic review. For the critical evaluation of systematic reviews or umbrella reviews (reviews of reviews) used to guide practice decisions, this checklist was created in 2017. The items mentioned in the checklist have enabled the reviewers to mark each one as unclear, applicable or not applicable. The reviewers chose to include, exclude, or seek further material in their overall evaluation of the paper they are reading based on the facts provided.

Statistical Analysis

Revman 5 software (Review Manager Web, The Cochrane Collaboration, Copenhagen, Denmark) was used in this meta-analysis. The pooled prevalence of stroke incidents was used by computing Cohen's d and weighing the risk rate in recruited studies. Random effect model was applied for calculating the odd ratios and I^2 test was applied for heterogeneity. Linear regression test of funnel plot asymmetry was used to evaluate the publication bias. Egger regression analysis was used to find out any bias and the *p*-value <0.05 was considered statistically significant.

Results

We included 12 related articles from the year 2004 to 2022. Five studies were conducted in the United States of America[19,22,23,25,28], three were from Germany[17,20,24], three were from Korea[18,21,27], and one was conducted on the Poland[26] population. Two recruited studies were prospective[17,20], 9 were retrospective[18,19,22-28], and one was unclear[21]. These 12 studies contained 26,276,857 participants. Out of these, 4,297 were affected by retinal artery occlusion. The largest sample size was reported in French et al[19] study, which included participants from national Medicare institutions. These studies incorporated patients of the age group 18-100 years. In 11 studies, subtypes of retinal artery occlusion were identified[17-25,27,28], while one study compared their results with the control group[26]. The inclusion criteria of studies involved neurologically symptomatic and asymptomatic cases and following the stroke guidelines provided by the American stroke association. In seven studies[18,19,20,22,24,25,27] MVL vision palette test was performed within 7 days, while fluorescein angiography was conducted in two studies[23,26]. In 10 studies[17,18,19,20,21,22,23,25,27,28] acute stroke cases were accessed *via* DW-MRI, while four studies[24,26,27,28] had unclear information. While assessing the neurological symptoms, only a single study[18] identified this variable (Table I).

A study by Roskal-Wałek et al[26] reported similar stroke incidents in hypertension enhanced the risk of stroke before and after RAO patients having a history of RAO than controls without any significant difference between both groups (*p*-value=0.567). During a 12-year follow-up, they observed no difference in incidents of ischemic stroke and all-cause mortality after an episode of RAO. Their Kaplen analysis shows a divergence of the curves. Tyler et al[27] reported 15% of strokes in the RAO group. They evaluated high exposure to hypertension, ischemic heart disease, atrial fibrillation, diabetes mellitus, chronic renal disease, and hyperlipidemia in RAO patients. The univariate analysis shows an increased risk of stroke during the ≤10-year follow-up (HR, 1.78; 95% CI, 1.32-2.41). In their study, increasing age was the major risk factor for stroke in RAO patients. They observed 38.9 cases of stroke per 1,000 person-years in ROA patients. Patients<65 years show a greater risk of stroke. Meanwhile, a study by French et al[19] diagnosed 49 CRAO cases with stroke in six months. In a study by Lavin et al[25], 37.3% of cases reported acute stroke out of 103 CRAO cases. Golsari et al[20] revealed ICA stenosis ≥50% ipsilateral to retinal ischemia in 19 patients. In their study, ICA was the silent factor of brain infarction. In Zhang et al[28], the stroke ratio was reported as 19.3%, while Lauda et al[24] reported 23% incidents of stroke. Comparing these results with Laczynski et al[23] study, they only had 2.3% incidents of acute stroke. Hong et al[21] reported 8.6% of incidents, while Choo et al[22] reported 2.2% of stroke incidents.

Meta-Analysis

For the meta-analysis, the pooled prevalence of stroke incidents was used by computing Cohen's d and weighing the risk rate in recruited studies. We used a random effect model for calculating the odd ratios. Then I^2 test was applied for heterogeneity. We observed 2% heterogeneity among studies indicating the variations in methodology and small sample size selection (Figure 2). One large cohort of French studies was extracted from the meta-analysis to formulate the results. All the studies reported a positive correlation. We observed a weak correlation between stroke risk and retinal artery occlusion in the study of Tyler et al[27], Callizo et al[17], Zhang et al[28], Lavin et al[25], French et al[19], and Lauda et al[24] (r=0.001, 0.01, 0.02, 0.05, 0.001, and 0.016 respectively). However, the remaining studies show a strong positive correlation between both variables. Egger regression analysis shows no biases as the *p*-value was greater than 0.05 (Egger regression test result: t=0.38, df=8, *p*-value=0.7130).

Discussion

A study based on administrative data[13] provided a stroke incidence estimate for patients with acute retinal artery occlusion of 1%, while a clinical investigation[24] reported a stroke incidence estimate of 37%[13,20,24-25,28]. Numerous factors, including the case definition and diagnostic imaging, may be responsible for this variation. Greater clinical significance would result from understanding this rate better. In addition, it would be beneficial to address the issue of the urgent need

Table I. Demographic characteristics, study descriptions, and design of the investigations selected for our systematic review.

Author (Year)	Region	Study design	Total number of participants	Age	Disease	Acute ischemia on dw-MRI	dw-MRI features	Neurologic symptoms
Callizo et al (2017)[17]	Germany	Prospective	77	24-75	77 CRAO	3 CRAO	ICA stenosis ≥70%	Not mentioned
Cho et al (2016)[18]	Korea	Retrospective	46	18-92	46 cases of BRAO	3 cases of BRAO	7.8% ischemic stroke	Not mentioned
French et al (2018)[19]	USA	Retrospective	26,275,521	–	3,338 cases of CRAO	49 CRAO cases reported stroke	Not mentioned	Not mentioned
Golsari et al (2017)[20]	Germany	Prospective	112	59-75	69 cases of CRAO 8 cases of BRAO	13 cases of CRAO and 2 cases of BRAO	70.6% ipsilateral to the involved eye,	Not mentioned
Ho-Hoong et al (2017)[21]	Korea	Unclear	151	60.8±15.3	119 cases of CRAO 32 cases of BRAO	119 CRAO 32 BRAO	6.6% ipsilateral to the RAO, 8.6% ischemic stroke	Not mentioned
Kevin et al (2021)[22]	USA	Retrospective	89	46-100	CRAO	–	2.2% ischemic stroke, 1.1% hemorrhage stroke 2.2% TIA	Not mentioned
Laczynski et al (2020)[23]	USA	Retrospective	221	66.1±15.1	100 CRAO 109 BRAO	Not mentioned	>50% carotid stenosis 2.3% stroke	Not mentioned
Lauda et al (2015)[24]	Germany	Retrospective	213	57-83	101 cases of CRAO 44 cases of BRAO	26 cases of CRAO 15 cases of BRAO	55% ipsilateral to the involved eye, single vascular territory 65.3%, an average of three lesions per patient	Shown in 3 cases of CRAO and 1 case of BRAO
Lavin et al (2018)[25]	USA	Retrospective	67	65.1±12.8	67 cases of CRAO	25 cases	76% ipsilateral to involved eye	Not mentioned
Roskal-Walek et al (2022)[26]	Poland	Retrospective	139	-	139 cases of ROA compared with the control group	14 cases	Not mentioned	Not mentioned
Tyler et al (2016)[27]	Korea	Retrospective nationwide	401	<50 to ≥80	119 CRAO	62 cases of RAO 32 cases of BRAO	Not mentioned	Not mentioned
Zhang et al (2018)[28]	USA	Retrospective	41	64.5±13.5	12 cases of CRAO 5 cases of BRAO	4 cases of CRAO and 2 cases of BRAO	Not mentioned	Not mentioned

*CRAO: central retinal artery occlusion; BRAO: Branch retinal artery occlusion; dw-MRI: Diffusion-weighted.

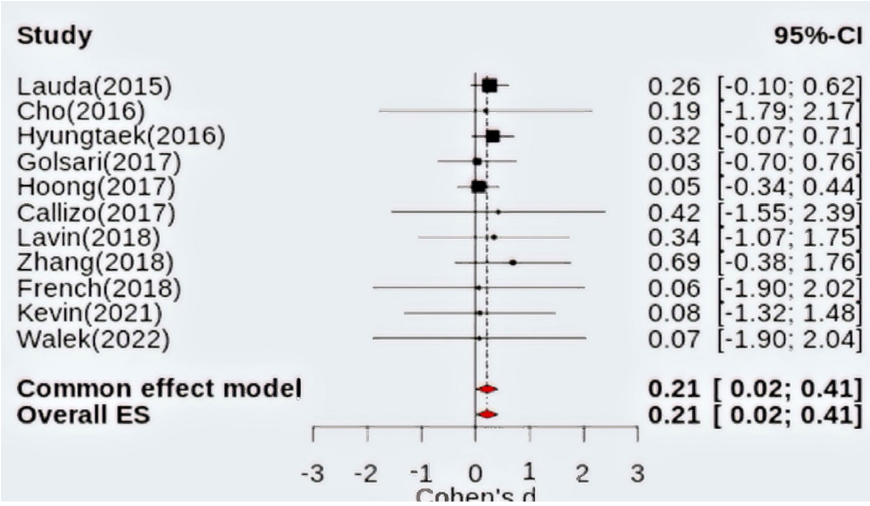

Figure 2. Fixed effect forest plot of studies selected for the systematic review.

for a neurological examination, allowing for improved illness management. Atrial fibrillation (AF) is more common in patients with CRAO than in controls which are age- and sex-matched[29], and CRAO predicts a greater risk of recurrent stroke in patients who already have AF[30]. A higher chance of finding AF in patients with CRAO is linked to longer cardiac monitoring[31].

According to a recent meta-analysis by Zhou et al[32], individuals with retinal artery occlusion have a twofold increased risk of cerebrovascular disorders compared to controls. Zhou et al[32] analysis did not rely on neuroimaging to identify the event an acute stroke occurs, and the interval between retinal artery closure and stroke onset was not taken into account. Despite having different control groups and populations (South Korean *vs.* US Medicare population), two sizable population-based studies found a statistically significant increase in the risk of stroke after CRAO, with an incidence ranging between 1.2 and 2.2% during the first seven days after CRAO[13,19]. Two previous studies[32,33] were based on administrative data-set reviews, so miscoding issues may have affected the results. In addition, regardless of symptoms, the lack of dw-MRI in all patients with CRAO did not allow the identification of silent ischemia, potentially underestimating its incidence. These factors may account for the lower brain ischemia incidence compared with our results.

Additionally, the absence of a control group in the studies included in this meta-analysis may have been a source of bias, which could have affected the findings. Given the remarkable ability dw-MRI has to analyze early ischemic damage in the brain, with a sensitivity and specificity totaling 88-100% and 95-100%, respectively[34,35], an overestimation of the event, however, seems unlikely. Additionally, MRIs performed within 7 days following MVL revealed evidence of acute cerebral infarction in up to 90% of individuals who did not exhibit any neurological symptoms[36]. The majority of ischemic cerebral infarctions caused by MVL are hence clinically silent. As a secondary result, we looked into the combined incidence of acute stroke in asymptomatic patients. The EXPRESS trial[30] and SOS-TIA study[37] showed that early diagnosis and fast treatment after transient ischemic attack and small stroke significantly (by 80%) decreased the risk of subsequent stroke. Similarly, we advise immediate brain imaging for patients with acute retinal artery occlusion under the supervision of a neurologist. Since the financial burden of referring these patients urgently to the emergency department or stroke center is outweighed by the economic and social costs produced by the disability and long-term care of stroke, this management may reduce the risk of stroke recurrence and would obviously benefit both the patient and the health care system[38].

On the one hand, Hayreh[14] claimed that immediate neurologic testing in patients with acute CRAO was pointless and expensive. The same author in another study[39] concluded that brain MRI was unhelpful in absence of neurological symptoms. By contrast, Arnold et al[40] advocated for a different strategy for treating acute CRAO, stating that there was a high chance of developing an asymptomatic acute ischemic stroke and that patients should be referred to a stroke unit or emergency room right away. According to the most recent American Academy of Ophthalmology recommendations[12], individuals with acute CRAO must be transported immediately to a stroke center or emergency room, and a neuroimaging examination must be completed within 24 hours[9]. However, clinical practice surveys revealed that 35% of ophthalmologists urgently referred CRAO patients to the ER[41, 42], while more than 80% of retina specialists recommended an outpatient workup[43].

Although the likelihood of stroke after retinal artery closure is well established, estimates of its occurrence are still disputed[40]. Unquestionably, a greater comprehension of the frequency of acute stroke within 7 days of an ischemic MVL diagnosis would reflect the clinical importance of the problem and, as a result, would help determine which strategy could be appropriate. Quite peculiarly, according to a survey of adults with normal vision assessing patients' preferences for the treatment of RAO, 39% of those adults would be willing to accept a small risk of stroke, and 37% would even be willing to accept a small risk of death to triple the likelihood of recovering 20/100 visual acuity in one eye when the unaffected eye is sighted[44]. If there is no sightedness in the unaffected eye, more than 80% of people would be willing to accept these risks[44].

Regarding limitations, the studies selected for our systematic review and subsequent meta-analysis showed a 2% heterogeneity, reflecting different methodologies and choices for small sample sizes. As a result, confounding and bias (such as selection or misclassification bias) may have been introduced. Also, there were few trials[24-26] that comprised comparatively few patients. Only two[17,30] of the investigations were prospective; the others were retrospective, and all the studies lacked controls. The presence of bias in the data is still unclear due to the lack of a control group, which does not clarify whether any variable may have impacted them. Nevertheless, because they all used dw-MRI, all of the included investigations exhibited equivalent techniques.

Conclusions

Our analysis demonstrates that those with RAO have a noticeably higher chance of experiencing an acute stroke than people without RAO. Furthermore, compared to people without RAO, patients with RAO, especially those under 75 years old, have a markedly increased risk of having an acute stroke following an occlusion episode. However, given that only a small number of the studies in our review did not show a clear correlation between the two, we believe more research is required to conclusively link RAO and the prevalence of acute stroke. This will allow for the development of a treatment strategy that may include prompt referral to the emergency room or stroke unit for neurological assessment and brain imaging as part of the clinical management of RAO.

Informed Consent

Not applicable.

Funding

This study is supported *via* funding from Prince Sattam bin Abulaziz University project number PSAU/2023/R/1444.

ORCID ID

O. Al Jarallah: 0000-0003-4285-8323

Conflict of Interest

The authors report no conflict of interest in preparing this systematic review and meta-analysis.

Ethics Approval

Not applicable.

Availability of Data and Materials

The data will be available with the corresponding author and can be accessed with request to the corresponding author *via* email.

Acknowledgements

The author would like to thank Prince Sattam bin Abulaziz University for support.

References

1) Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV; American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013; 44: 2064-2089.

2) Hayreh SS, Zimmerman MB. Central retinal artery occlusion: visual outcome. Am J Ophthalmol 2005; 140: 376-391.

3) Leavitt JA, Larson TA, Hodge DO, Gullerud RE. The incidence of central retinal artery occlusion in Olmsted County, Minnesota. Am J Ophthalmol 2011; 152: 820-823.

4) Park SJ, Choi NK, Seo KH, Park KH, Woo SJ. Nationwide incidence of clinically diagnosed central retinal artery occlusion in Korea, 2008 to 2011. Ophthalmology 2014; 121: 1933-1938

5) Kido A, Tamura H, Ikeda HO, Miyake M, Hiragi S, Tsujikawa A. Nationwide incidence of central retinal artery occlusion in Japan: an exploratory, descriptive study using the National Database of Health Insurance Claims (2011-2015). BMJ Open 2020; 10: e041104.

6) Schumacher M, Schmidt D, Jurklies B, Gall C, Wanke I, Schmoor C, Maier-Lenz H, Solymosi L, Brueckmann H, Neubauer AS, Wolf A, Feltgen N; EAGLE-Study Group. Central retinal artery occlusion: local intra-arterial fibrinolysis versus conservative treatment, a multicenter randomized trial. Ophthalmology 2010; 117: 1367-1375.

7) Cugati S, Wang JJ, Rochtchina E, Mitchell P. Ten-year incidence of retinal emboli in an older population. Stroke 2006; 37: 908-910.

8) Schorr EM, Rossi KC, Stein LK, Park BL, Tuhrim S, Dhamoon MS. Characteristics and outcomes of retinal artery occlusion: nationally representative data. Stroke 2020; 51: 800-807.

9) Biousse V, Newman N. Retinal and optic nerve ischemia. Continuum 2014; 20: 838-856.

10) Hayreh SS, Podhajsky PA, Raman R, Zimmerman B. Giant cell arteritis: validity and reliability of various diagnostic criteria. Am J Ophthalmol 1997; 123: 285-296.

11) Hayreh SS. Acute retinal arterial occlusive disorders. Prog Retin Eye Res 2011; 30: 359-394.

12) Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, Hatsukami TS, Higashida RT, Johnston SC, Kidwell CS, Lutsep HL, Miller E, Sacco RL; American Heart Association; American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Interdisciplinary Council on Peripheral Vascular Disease. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009; 40: 2276-2293.

13) Park SJ, Choi NK, Yang BR, Park KH, Lee J, Jung SY, Woo SJ. Risk and Risk Periods for Stroke and Acute Myocardial Infarction in Patients with Central Retinal Artery Occlusion. Ophthalmology 2015; 122: 2336-2343.

14) Hayreh SS. Do patients with retinal artery occlusion need an urgent neurological evaluation? Am J Ophthalmol 2018; 196: 53-56.

15) Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009; 6: e1000100.

16) Aromataris E, Fernandez R, Godfrey C, Holly C, Kahlil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct, and reporting of an Umbrella review approach. Int J Evid Based Healthc 2015; 13: 32-40.

17) Callizo J, Feltgen N, Ammermann A, Ganser J, Bemme S, Bertelmann T, Pfeiffer S, Duvinage A, Gröschel K, Hoerauf H, Wachter R. Atrial fibrillation in retinal vascular occlusion disease and non-arteritic anterior ischemic optic neuropathy. PLoS One 2017; 12: e0181766.

18) Chodnicki Kevin D, Tanke LB, Pulido JS, Hodge DO, Klaas JP, Olsen TW, Bhatti MT, Chen JJ. Stroke Risk before and after Central Retinal Artery Occlusion: A Population-based Analysis. Ophthalmology 2021; 129: 203-208.

19) 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: 125-131.

20) Golsari A, Bittersohl D, Cheng B, Griem P, Beck C, Hassenstein A, Nedelmann M, Magnus T, Fiehler J, Gerloff C, Thomalla G. Silent Brain Infarctions and Leukoaraiosis in Patients With Retinal Ischemia A Prospective Single-Center Observational Study. Stroke 2017; 48: 1392-1396.

21) Hong JH, Sohn SI, Kwak J, Yoo J, Ahn SJ, Woo SJ, Jung C, Yum KS, Bae HJ, Chang JY, Jung JH, Lee JS, Han MK. Retinal artery occlusion and associated recurrent vascular risk with underlying etiologies. PLoS One 2017; 12: e0177663.

22) Cho KH, Kim CK, Woo SJ, Park KH, Park SJ. Cerebral Small Vessel Disease in Branch Retinal Artery Occlusion. Invest Ophthalmol Vis Sci 2016; 57: 5818-5824.

23) Laczynski DJ, Gallop J, Lyden SP, Bena J, Yuan A, Smolock CJ, Caputo FJ. Retinal artery occlusion does not portend an increased risk of stroke. J Vasc Surg 2020; 72: 198-203.

24) Lauda F, Neugebauer H, Reiber L, Jüttler E. Acute Silent Brain Infarction in Monocular Visual Loss of Ischemic Origin. Cerebrovasc Dis 2015; 40: 151-156.

25) Lavin P, Patrylo M, Hollar M, Kiersten BE, Kirshner H, Schrag M. Stroke Risk and Risk Factors in Patients with Central Retinal Artery Occlusion. Am J Ophthalmol 2018; 196: 96-100.

26) Roskal-Wałek J, Wałek P, Biskup M, Sidło J, Cieśla E, Odrobina D, Mackiewicz J, Wożakowska-Kapłon B. Retinal Artery Occlusion and Its Impact on the Incidence of Stroke, Myocardial In-

farction, and All-Cause Mortality during 12-Year Follow-Up. J Clin Med 2022; 11: 4076.

27) Tyler Hyungtaek Rim, Jinu Han, Yoon Seong Choi, Seung-sik Hwang, Christopher Seungkyu Lee. Retinal Artery Occlusion and the Risk of Stroke Development Twelve-Year Nationwide Cohort Study. Stroke 2016; 47: 376-382.

28) Zhang LY, Zhang J, Kim RK, Matthews JL, Rudich DS, Greer DM, Lesser RL, Amin H. Risk of Acute Ischemic Stroke in Patients With Monocular Vision Loss of Vascular Etiology. J Neuroophthalmol 2018; 38: 328-333.

29) Kewcharoen J, Tom ES, Wiboonchutikula C, Trongtorsak A, Wittayalikit C, Vutthikraivit W, Prasitlumkum N, Rattanawong P. Prevalence of atrial fibrillation in patients with retinal vessel occlusion and its association: a systematic review and meta-analysis. Curr Eye Res 2019; 44: 1337-1344.

30) Christiansen CB, Lip GY, Lamberts M, Gislason G, Torp-Pedersen C, Olesen JB. Retinal vein and artery occlusions: a risk factor for stroke in atrial fibrillation. J Thromb Haemost 2013; 11: 1485-1492.

31) Watson RA, Wellings J, Hingorani R, Zhan T, Frisch DR, Ho RT, Pavri BB, Sergott RC, Greenspon AJ. Atrial fibrillation post central retinal artery occlusion: role of implantable loop recorders. Pacing Clin Electrophysiol 2020; 43: 992-999.

32) Zhou Y, Zhu W, Wang C. Relationship between retinal vascular occlusions and incident cerebrovascular diseases: A systematic review and meta-analysis. Medicine 2016; 95: e4075.

33) Goldstein LB. Accuracy of ICD-9-CM coding for the identification of patients with acute ischemic stroke. Effect of modifier codes. Stroke 1998; 29: 1602-1604.

34) Fiebach JB, Schellinger PD, Jansen O, Meyer M, Wilde P, Bender J, Schramm P, Jüttler E, Oehler J, Hartmann M, Hähnel S, Knauth M, Hacke W, Sartor K. CT and diffusion-weighted MR imaging in randomized order: diffusion-weighted imaging results in higher accuracy and lower interrater variability in the diagnosis of hyperacute ischemic stroke. Stroke 2002; 33: 2206-2210.

35) González RG, Schaefer PW, Buonanno FS, Schwamm LH, Budzik RF, Rordorf G, Wang B, Sorensen AG, Koroshetz WJ. Diffusion-weighted MR imaging: diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset. Radiology 1999; 210: 155-162.

36) Lee J, Kim SW, Lee SC, Kwon OW, Kim YD, Byeon SH. Cooccurrence of acute retinal artery occlusion and acute ischemic stroke: Diffusion-weighted magnetic resonance imaging study. Am J Ophthalmol 2014; 157: 1231-1238.

37) Lavallée PC, Meseguer E, Abboud H, Cabrejo L, Olivot JM, Simon O, Mazighi M, Nifle C, Niclot P, Lapergue B, Klein IF, Brochet E, Steg PG, Lesèche G, Labreuche J, Touboul PJ, Amarenco P. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet Neurol 2007; 6: 953-960.

38) Mukundan G, Seidenwurm DJ. Economic and Societal Aspects of Stroke Management. Neuroimaging Clin N Am 2018; 28: 683-689.

39) Hayreh SS, Zimmerman MB. Ocular arterial occlusive disorders and carotid artery disease. Ophthalmol Retin 2017; 1: 12-18.

40) Arnold AC. Urgent evaluation of the patient with acute central retinal artery occlusion. Am J Ophthalmol 2018; 196: 106-107.

41) Atkins E, Bruce BB, Newman NJ, Biousse V. Translation of clinical studies to clinical practice: a survey on the treatment of central retinal artery occlusion. Am J Ophthalmol 2009; 148: 172-173.

42) Youn TS, Lavin P, Patrylo M, Schindler J, Kirshner H, Greer DM, Schrag M. Current treatment of central retinal artery occlusion: a national survey. J Neurol 2018; 265: 330-335.

43) Abel AS, Suresh S, Hussein HM, Carpenter AF, Montezuma SR, Lee MS. Practice patterns after acute embolic retinal artery occlusion. Asia Pac J Ophthalmol 2017; 6: 37e39.

44) Chia EM, Mitchell P, Rochtchina E, Foran S, Wang JJ. Unilateral visual impairment and health-related quality of life: the Blue Mountains Eye Study. Br J Ophthalmol 2003; 87: 392-395.