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Is there an association between retinal vein occlusion and cerebrovascular accident? A systematic review and meta-analysis

Kai-Yang Chen[1], Hoi-Chun Chan[2] and Chi-Ming Chan[3,4*]

Abstract

Background Retinal vein occlusion (RVO) is a significant retinal vascular disorder that has been hypothesized to increase the risk of cerebrovascular accidents (CVA). Given the shared vascular pathology between the retina and cerebral circulation, understanding the association between RVO and stroke incidence is critical for early intervention and risk management. This systematic review and meta-analysis aim to evaluate the risk of CVA, including ischemic and hemorrhagic subtypes, in patients with RVO.

Methods This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered in PROSPERO (CRD42024557820). A systematic search of PubMed, Cochrane Library, Scopus, Web of Science, and Embase was conducted from inception to February 2025. Studies assessing the incidence of CVA post-RVO in adult patients (≥ 18 years) were included. Two independent reviewers performed study selection, data extraction, and quality assessment using the Cochrane Risk of Bias tool for Non-Randomized studies (ROBINS-I) was used for observational cohort studies. Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) software version 3.7, applying a fixed-effects model for low heterogeneity. Subgroup and sensitivity analyses were performed based on RVO type (BRVO vs. CRVO) and stroke subtype (ischemic vs. hemorrhagic CVA). Publication bias was evaluated using Egger's test and funnel plots.

Results A total of 14 studies ($n = 97,812$ patients) were included. The pooled event rate for CVA post-RVO was 37.5% (95% CI: 37.3%–37.8%), with no significant heterogeneity ($I^2 = 0\%$, $p = 0.97$). Subgroup analysis showed that both ischemic CVA (37.8%; 95% CI: 37.3%–38.3%) and hemorrhagic CVA (32.7%; 95% CI: 32.3%–33.1%) occurred at similar rates across branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO).

The mortality rate post-CVA in RVO patients was 69.0% (95% CI: 68.4%–69.5%), highlighting the severity of stroke outcomes in this population. The incidence of ischemic cardiovascular events, including myocardial infarction, was 15.7% (95% CI: 15.4%–16.0%), reinforcing the need for cardiovascular monitoring in RVO patients. The incidence of deep vein thrombosis (DVT) was relatively low (0.05%) but still warrants clinical attention in high-risk populations.

Publication bias was minimal, as confirmed by Egger's test ($p > 0.24$) and funnel plot symmetry. Sensitivity analyses confirmed the robustness of the pooled estimates.

Conclusion This meta-analysis provides strong evidence linking RVO to an increased risk of CVA and mortality. Given the high incidence of stroke (37.5%) and mortality post-CVA (69%), early cardiovascular risk assessment

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and intervention are crucial. Patients with RVO should undergo comprehensive vascular risk evaluation, including blood pressure control, lipid regulation, and anticoagulation therapy when indicated. The findings support a multidisciplinary approach involving ophthalmologists, neurologists, and cardiologists for proactive stroke prevention strategies in RVO patients. Future research should explore genetic predispositions, inflammatory markers, and AI-based predictive models to improve early risk stratification and intervention.

Keywords Retinal vein occlusion, Cerebrovascular accident, Ischemic stroke, Hemorrhagic stroke, Cardiovascular risk, Mortality, Meta-analysis

Introduction

Among retinal vascular disease, Retinal vein occlusion remains the second leading cause of vision loss without pain in middle-aged and older adults by affecting 48 patients per 0.1 million person-years in total and 136.09 in those 50 and above according to statistical records [1]. The retinal vein occlusion (RVO) exists in two specific subtypes that distinguish branch retinal vein occlusion (BRVO) from central retinal vein occlusion (CRVO) of which BRVO causes blockage in smaller retinal veins, while CRVO blocks blood drainage in the central retinal vein to create different levels of vision problems and additional complications for patients [2].

CVA is a significant worldwide public health issue that can cause various complications [3]. Globally, CVA ranks as the second most prevalent cause of death and disability, according to the World Health Organization (WHO) where chronic issues severely strain CVA survivors [4]. According to a recent investigation, the European population's crude CVA prevalence was 18.5 per 1,000 people, but the adjusted prevalence, which took age and sex distribution into account, was 9.6 per 1,000 people [5]. Individuals exhibit notable limitations, impairments, and behavioral and cognitive changes despite becoming functionally independent again. CVA is a common disease that impairs many aspects of life and alters the body, mind, and numerous cognitive and psychological functions [6]. Research has demonstrated that the anatomical and physiological features of retinal blood arteries are comparable to those of cerebral vessels [7]. Similarly, some systemic risk factors for RVO are linked to arterial thromboembolic events, including myocardial infarction and cerebrovascular disease [8, 9]. After controlling relevant confounders, a new population-based, longitudinal investigation identified a substantial correlation between RVO and the risk of CVA [10, 11]. The results of a registry-based cohort analysis also showed that central RVO was linked to a higher risk of CVA [12]. CVD was more prevalent among patients with retinal vascular blockage than among healthy adults of all ages [13].

This study aims to systematically evaluate and quantify the previously underexplored association between retinal vein occlusion (RVO) and cerebrovascular accident (CVA), including both ischemic and hemorrhagic stroke subtypes. By synthesizing data from multiple high-quality studies, this meta-analysis seeks to determine the incidence, risk factors, and clinical outcomes of CVA in patients with RVO, while also assessing its impact on mortality rates and cardiovascular comorbidities, an aspect that has received limited attention in prior research. Additionally, the study provides a comparative risk assessment between branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO), offering new insights into potential variations in cerebrovascular outcomes based on RVO subtype. This research also examines the incidence of ischemic cardiovascular events, such as myocardial infarction and deep vein thrombosis (DVT), positioning RVO as a possible systemic vascular risk marker beyond its ophthalmic implications. Employing advanced meta-analytical techniques, including subgroup analyses and meta-regression, this study ensures greater precision and reliability in risk estimation. By highlighting RVO as a potential early predictor of stroke, this study underscores the necessity for multidisciplinary screening and preventive strategies involving ophthalmologists, neurologists, and cardiologists, aiming to shift the clinical perspective toward proactive cerebrovascular risk mitigation in RVO patients.

Methodology

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14] and Cochrane Handbook [15] for conducting this systematic review and meta-analysis. T Our systematic review has been registered on an online registration website, PROSPERO, the number is CRD42024557820.

Search strategy

Two reviewers (K. Y. C. and H. C. C.) comprehensively searched for eligible studies from MEDLINE (PubMed), Central (Cochrane Library), Scopus, Web of Science and Embase (Ovid) databases from inception to February 5th, 2025, focusing on Randomized controlled trials and cohort studies identifying the incidence of

Cerebrovascular Accident in Retinal Vein Occlusion. A detailed description of the keywords with Boolean operators used for each database are provided in Supplementary Table 1. No language restriction was applied. Reference lists of all eligible trials were also searched to identify other studies. Duplicate studies were eliminated using EndNote 20.2.1 (Clarivate Analytics, Philadelphia, PA). The electronic databases PubMed, Embase, Scopus, Web of Science and Cochrane Library were selected for their extensive coverage of clinical and systematic reviews, providing relevant peer-reviewed studies on imaging techniques.

Study selection

Study selection followed the PICOS (Participants, Intervention, Comparisons, Outcomes, and Study Design) framework to ensure a structured and systematic approach. Studies were included if they focused on adult patients (≥18 years) diagnosed with retinal vein occlusion (RVO), including branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). The included studies specifically evaluated the incidence of cerebrovascular accident (CVA) following RVO, along with associated cardiovascular complications such as ischemic heart disease and deep vein thrombosis (DVT). Eligible studies assessed the risk of CVA (both ischemic and hemorrhagic) as a primary outcome, as well as secondary outcomes such as mortality rates, incidence of ischemic cardiovascular events, and thromboembolic complications. Studies were included if they reported quantitative data on CVA incidence post-RVO, stratified by RVO subtype (BRVO vs. CRVO), or if they provided subgroup analyses based on stroke type. Comparative studies involving non-RVO populations or general cardiovascular cohorts were included to assess relative risk. Only peer-reviewed randomized controlled trials (RCTs), cohort studies, or case–control studies with a well-defined methodology and quantitative data were considered. There were no restrictions on geographic location or language to ensure a comprehensive review. Studies were excluded if they involved pediatric populations, animal models, in vitro studies, or interventions unrelated to RVO and CVA risk. Case reports, conference abstracts, narrative reviews, and editorials were excluded due to insufficient methodological rigor. Additionally, studies with insufficient quantitative data, lack of comparator groups, or unclear reporting of CVA incidence were not included. Patients with pre-existing neurological disorders, systemic infections, or underlying conditions that could confound the relationship between RVO and CVA risk were not considered. Furthermore, studies focusing solely on ophthalmic outcomes without assessing cerebrovascular risks were excluded to maintain the review's focus on systemic complications following RVO.

Data collection and quality evaluation

Two reviewers (K. Y. C. and H. C. C.) independently screened titles and abstracts using EndNote 20.2.1, followed by full-text review of potentially eligible studies. Disagreements were resolved through consultation with a third author. Data were extracted into a pre-tested Microsoft Excel sheet, capturing details such as study design, sample size, demographics, interventions, and outcomes (e.g., IOP reduction, adverse events). Two complementary instruments were utilized to assess the quality of the included studies: the Cochrane Risk of Bias tool for RCTs for observational studies. The risk of bias was independently evaluated by two reviewers (K. Y. C. and H. C. C.), with any discrepancies resolved through consultation with a third reviewer (C. M. C.). The Cochrane Handbook for Systematic Reviews of Interventions, version 2.0, evaluates five domains: bias due to missing outcome data, bias due to deviations from intended interventions, bias from the randomization process, bias in selecting reported results, and bias in outcome measurement[16]. Each domain was classified as having a low risk of bias, some concerns regarding risk of bias, or a high risk of bias. The overall quality of each study was determined by summing the ratings across these five domains.

Statistical analysis

The statistical analysis was performed using Comprehensive Meta-Analysis (CMA) software version 3.7, following a detailed methodology to synthesize data from included studies. A random-effects model was applied for outcomes with significant heterogeneity ($I^2 > 75\%$), accounting for variability across populations, methodologies, and study designs. For outcomes with low heterogeneity ($I^2 \leq 75\%$), a fixed-effects model was used to provide precise estimates. Event rates with 95% confidence intervals (CIs) were calculated for categorical outcomes, such as the incidence of cerebrovascular accidents (CVA) following retinal vein occlusion (RVO), mortality rates, and cardiovascular comorbidities. Heterogeneity was assessed using the I^2 statistic, where values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively. Statistical significance was determined using Z-tests, with p-values < 0.05 considered statistically significant. To detect potential publication bias, funnel plots and Egger's test were employed, and additional sensitivity analyses were conducted by systematically removing individual studies to evaluate the robustness of the pooled results. Subgroup analyses were performed based on RVO type (BRVO vs. CRVO)

and CVA subtype (ischemic vs. hemorrhagic) to explore potential sources of heterogeneity. Meta-regression analysis was conducted to assess the influence of key covariates such as patient age, baseline cardiovascular risk factors, and study sample size on pooled effect estimates.

Results

Study characteristics

The flowchart (Fig. 1) presents the systematic selection process of studies for a review, following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The process is divided into two main pathways: identification through databases and registers, and identification through other methods. From databases such as PubMed, Embase, Web of Science, Scopus, and Cochrane, a total of 522 records were initially identified. Before screening, 94 duplicate records, 79 ineligible records marked by automation tools, and 207 records removed for other reasons were excluded, leaving 142 studies for screening. After excluding 39 records, 103 reports were sought for retrieval, but 21 could not be obtained. Out of the 82 reports assessed for eligibility, 68 were excluded due to invalid outcomes in 34 cases, invalid patient populations in 3 cases, invalid study designs in 22 cases, and invalid interventions in 9 cases, resulting in 14 studies included in the final review. Separately, other methods such as website searches and citation searching identified 33 records. After retrieval attempts, 4 reports could not be obtained, and the remaining 29 were assessed but excluded for not meeting inclusion criteria, contributing no additional studies. Ultimately, 14 studies were included in the review[17–30]. Table 1 describes the characteristics of included studies.

Risk of bias

The risk of bias assessment for the included studies was conducted across seven key domains is depicted in Fig. 2. Most studies demonstrated a low risk of bias across these domains, ensuring reliable and robust data. However, moderate risks of bias were noted in specific domains for several studies. Ho et al. (2009), DiCapua et al. (2012), and Park et al. (2015) exhibited moderate risk in D1 (bias due to confounding) due to the potential influence of unmeasured variables such as patient comorbidities or socioeconomic factors. Confounding can compromise the validity of the results if not properly adjusted for. Ahmed et al. (2015) and Bertelsen et al. (2012) showed moderate bias in D5 (missing data), which may be attributed to incomplete data collection or loss to follow-up, affecting the accuracy and generalizability of the findings. Ho et al. (2009) and Shih et al. (2015) displayed moderate risk in D7 (bias in selection of the reported result), suggesting selective reporting of outcomes that could overstate significant findings. Additionally, Ahmed et al. (2015) showed moderate bias in D4 (deviations from

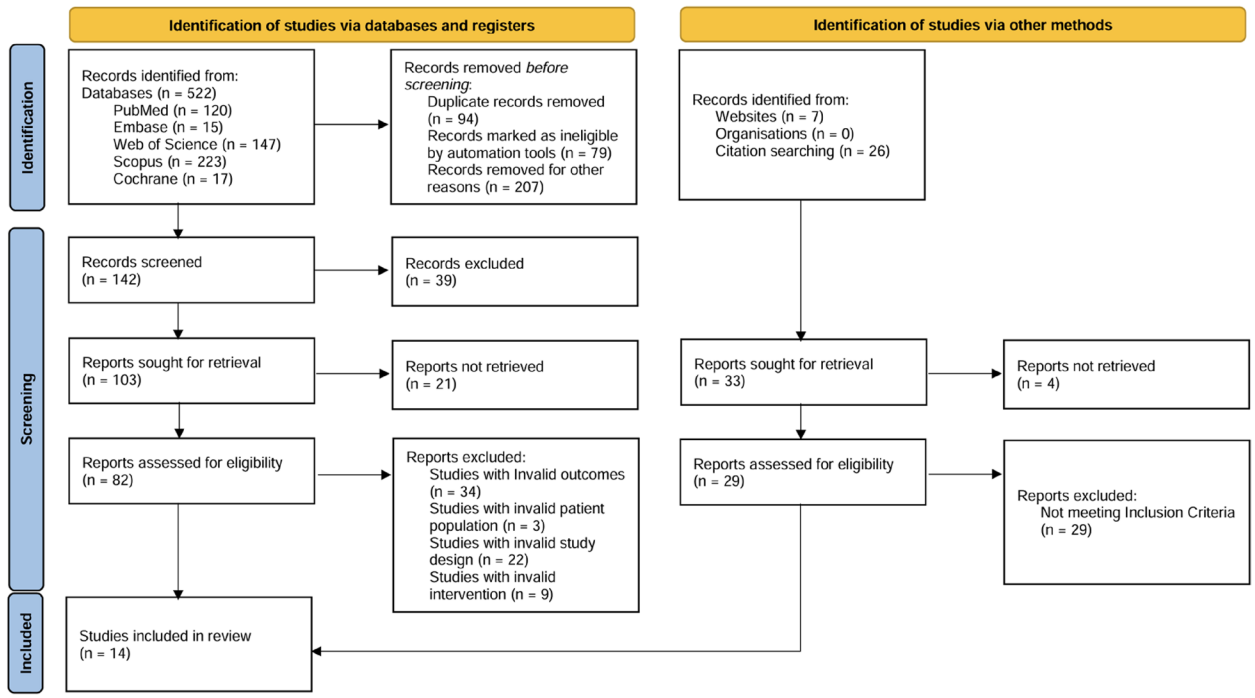

Fig. 1 PRISMA flow chart

Table 1 Characteristics of the included studies

Study ID	Location	Study design	Population	Follow-up	RVO types	Outcomes	Conclusion
Ho et al. (2009) [17]	Taiwan	Retrospective Population-based	RVO Group (*n* = 350), Control (*n* = 2100)	5 years	CRVO, BRVO	Stroke	There was no discernible correlation between RVO and an elevated risk of stroke
Werther (2011) [18]	USA	Retrospective Population-based	RVO Group (*n* = 4500), Comparison Group(*n* = 13,500)	3 years	CRVO, BRVO	MI, CVA	The cerebrovascular mortality rate was higher in those with RVO
Bertelsen et al. (2012) [19]	Denmark	Prospective Hospital-based	BRVO Group (*n* = 1168), Comparison Group (*n* = 116,800)	7 years	BRVO	Cerebrovascular Disease, MI	Patients remained at higher risk of developing cerebrovascular illness after the diagnosis
Di Capua et al. (2012) [20]	Italy	Retrospective Hospital-based	RVO Group (*n* = 45), Comparison Group (n = 145)	8 years	CRVO, BRVO	Acute Coronary Syndrome (ACS). Transient Ischemic Attack (TIA)	RVO and Stroke/TIA showed a significant correlation but not with ACS
Bertelsen et al. (2014) [21]	Denmark	Prospective Population-based	CRVO Group (*n* = 439), Comparison Group (n = 2195)	5.1 years & 5.7 years	CRVO	Cerebrovascular Disease, MI	There was a high death rate
El-Adly et al. (2015) [27]	Egypt	Prospective case–control study	RVO Group (*n* = 20), Control Group(*n* = 20)	1 year	CRVO, BRVO	Cerebrovascular accidents, stenosis of the ipsilateral internal carotid artery	Patients with RVO had a significantly higher risk of CVAs compared to the control group, likely due to increased stenosis in the ipsilateral ICA
Rim et al. (2015) [31]	South Korea	Prospective Population-based	RVO Group (n = 1031), Comparison Group(n = 5074)	9 years	CRVO, BRVO	Ischemic and hemorrhagic stroke	RVO was associated with a higher risk of hemorrhagic stroke and ischemic stroke, but not considerably
Shih et al. (2015) [22]	Taiwan	Prospective Population-based	*n* = 1,784,960	5 years	CRVO, BRVO	MI, stroke, peripheral artery disease (PAD), peripheral venous disease, diabetes mellitus (DM), death	There was an insignificant difference in the risk of stroke in patients with BRVO
Park et al. (2015) [23]	Korea	Case–Control Study	*n* = 44,603	1 year	Not reported	Ischemic and hemorrhagic stroke	RVO was associated with a high risk of stroke
Chen et al. (2018) [24]	Taiwan	Cohort Study	RVO Group (*n* = 22,919), Comparison Group (*n* = 114,595)	12 years	CRVO, BRVO	Strokes, including ischemic and hemorrhagic strokes and all-cause mortality	RVO significantly increased the risk of stroke, ischemic stroke, and hemorrhagic stroke. However,all-cause mortality was comparable with the control group

Table 1 (continued)

Study ID	Location	Study design	Population	Follow-up	RVO types	Outcomes	Conclusion
Nemet et al. (2024)[28]	Israel	Retrospective Cohort Study	$n=83$	1 year	CRVO, BRVO	Association between CHA_2DS_2-VASc score and visual prognosis	Higher CHA_2DS_2-VASc scores (≥ 6) were associated with worse visual prognosis after RVO despite anti-VEGF treatment
Wai et al. (2024)[25]	USA	Retrospective Cohort Study	$n=45,304$	10 years	Not reported	Relative risk of death, stroke, MI, DVT, and PE	RVO was associated with a higher risk of stroke
Zhang et al. (2024)[29]	European descent	Retrospective Cohort Study	RVO Group ($n=572$), Comparison Group ($n=255,766$)	10 years	CRVO, BRVO	Genetic liability of RVO and CVA Relative risk of ischemic stroke	RVOs are linked to IS, MI, and CES. Possible shared genetics with CVDs need further validation
Lusk et al. (2025)[30]	USA	Retrospective Cohort Study	$n=1,090,144$	1 year	CRVO	Relative risk of CIS and CRVO	RVOs are linked to IS

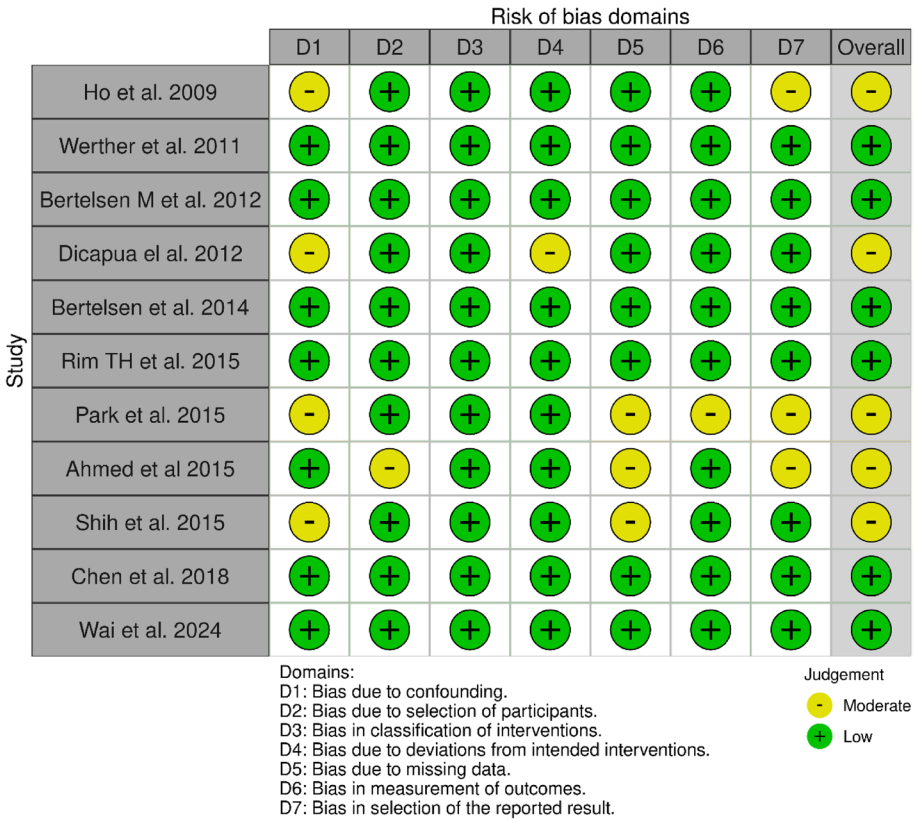

Fig. 2 Traffic light plots on risk of bias assessment

intended interventions), which might have resulted from variations in the intervention process, reducing the study's internal validity.

The summary plot in Fig. 3 illustrates the risk of bias assessment across multiple studies, categorizing them into low risk (green) and moderate risk (yellow). The domains assessed include bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. Most studies exhibit a low risk of bias, but certain domains, particularly selection of the reported result and missing data, have a notable proportion of studies categorized under moderate risk. The overall risk of bias also indicates a combination of both low and moderate-risk studies, reflecting variations in study design and methodology.

The studies contributing to moderate bias mainly show concerns in selection bias, missing data, and deviations from intended interventions. Selection bias arises from inadequate randomization or inappropriate inclusion criteria, leading to a non-representative sample. Missing data is another source of moderate bias, often resulting from incomplete follow-up or poor data collection strategies, potentially affecting study conclusions. Bias due to deviations from intended interventions is seen in studies where participant adherence to protocols was suboptimal or where unplanned co-interventions influenced the outcomes. Additionally, some studies exhibit reporting bias, where selective outcome reporting skews the interpretation of results. These biases highlight methodological challenges in study design, requiring robust strategies like rigorous randomization, comprehensive data handling, and pre-specified outcome reporting to enhance reliability.

Incidence of CVA post RVO

The forest plot in Fig. 4 presents a meta-analysis on the incidence of CVA following RVO. The pooled event rate for CVA incidence across 10 studies is 0.375 (95% CI: 0.373–0.378), indicating that approximately 37.5% of patients with RVO may experience a CVA. The analysis shows no significant heterogeneity among studies, as evidenced by an I^2 value of 0% and a high p-value ($p = 0.97$), confirming consistency in the findings. Both fixed-effects and random-effects models yield the same point estimate (0.375), reinforcing the reliability of the results.

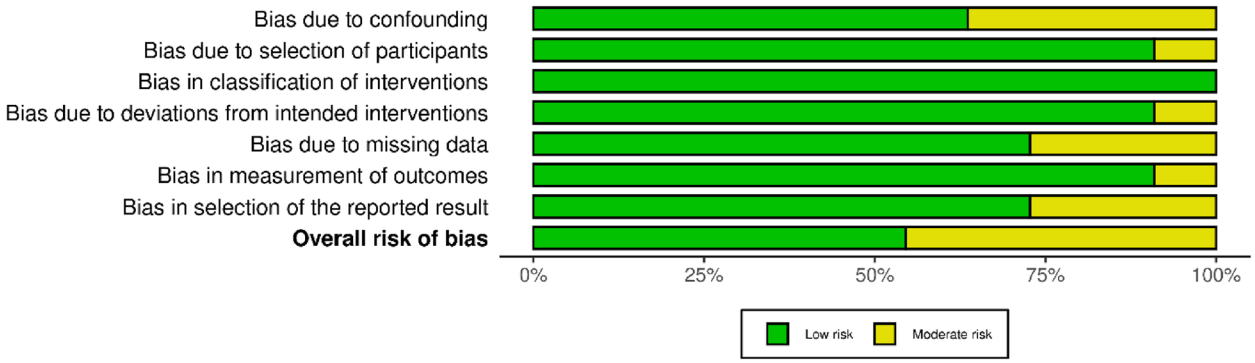

Fig. 3 Summary plots on risk of bias assessment

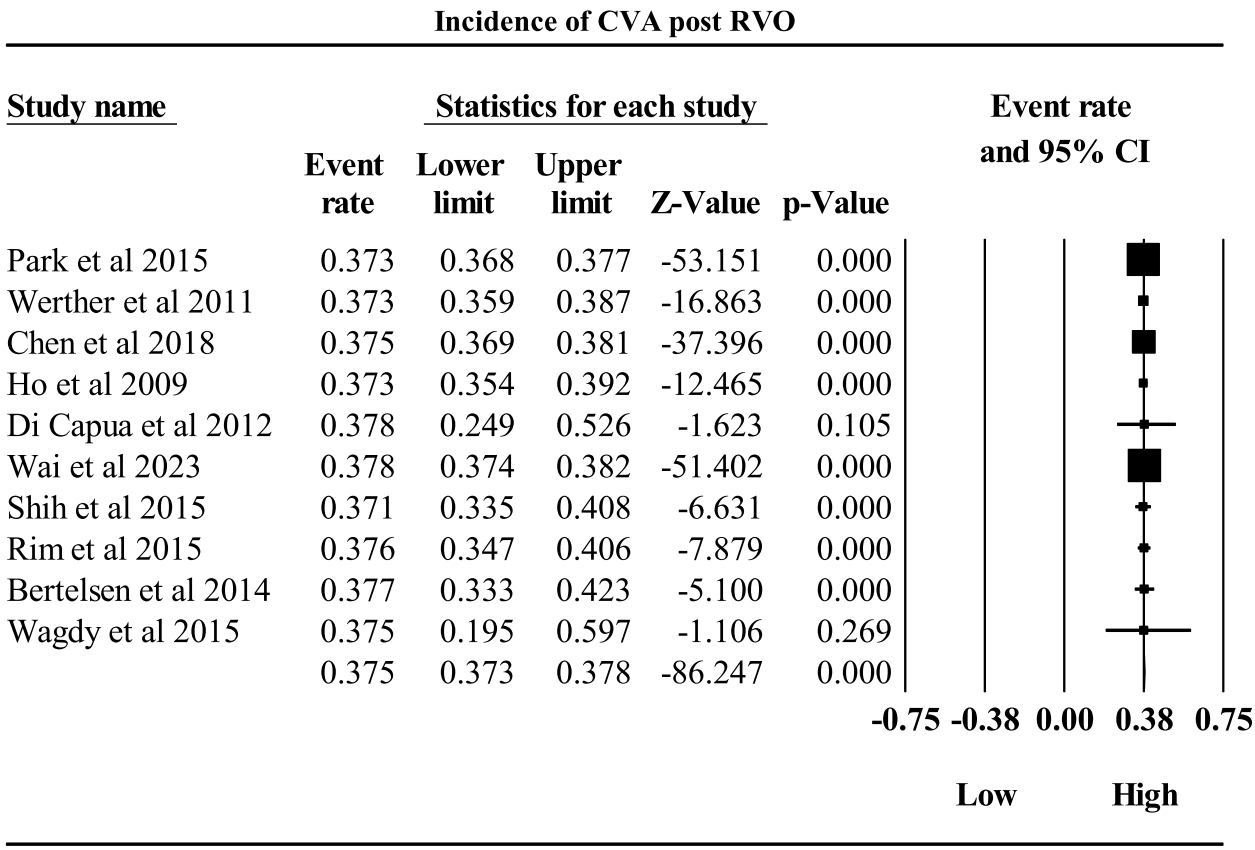

Fig. 4 Forest Plot on Incidence of CVA post RVO

Notably, studies with substantial contributions to the overall effect size include Wai et al. (2023), Chen et al. (2018), and Park et al. (2015), which reported event rates close to the pooled estimate, enhancing its precision. Conversely, studies like Di Capua et al. (2012) and Wagdy et al. (2015) exhibit wider confidence intervals and relatively lower weights, suggesting variability in their outcomes.

Clinically, these findings underscore the importance of vigilant cardiovascular monitoring and early intervention in patients diagnosed with RVO. The relatively high event rate highlights the significant risk of subsequent CVA in this population, emphasizing the need for multidisciplinary management strategies to prevent stroke and improve patient outcomes.

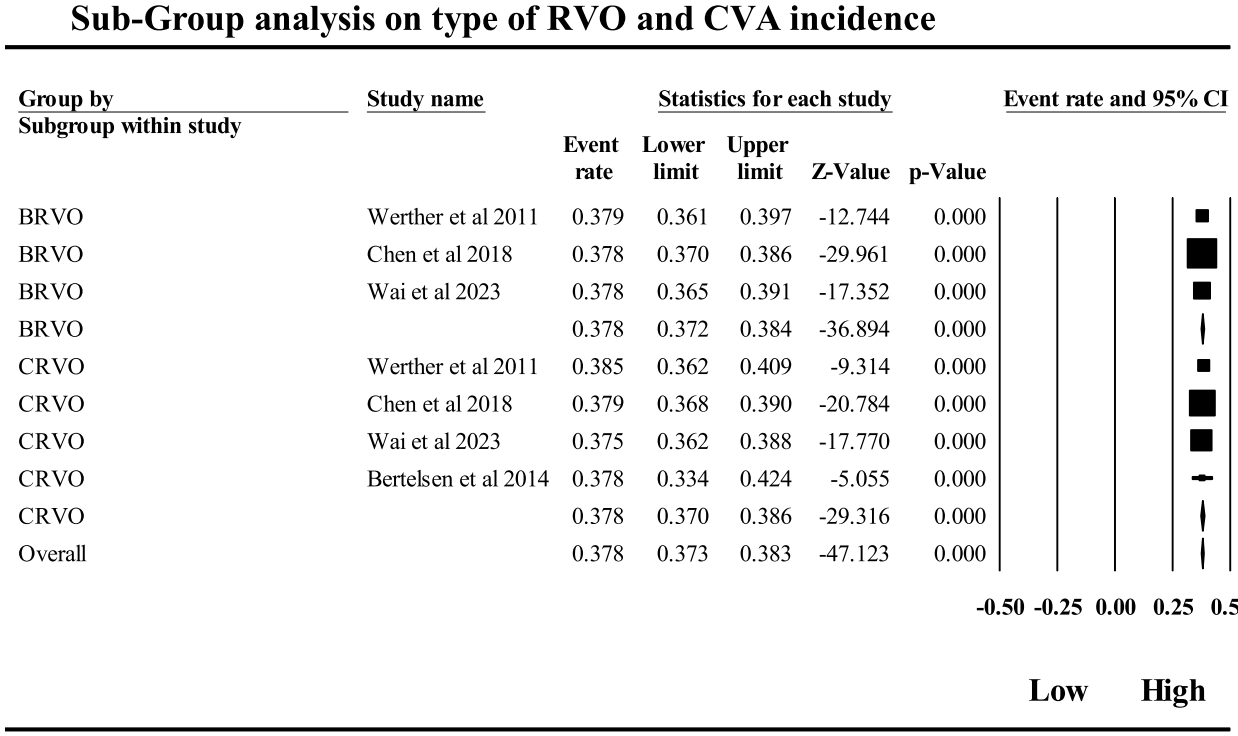

Fig. 5 Forest plot on sub-group analysis on the incidence of ischemic CVA based on type of RVO

Sub-group analysis on the incidence of ischemic CVA based on type of RVO

The forest plot in Fig. 5 presents a subgroup meta-analysis on the incidence of CVA following RVO, categorized into BRVO and CRVO. The overall pooled event rate for CVA is 0.378 (95% CI: 0.373–0.383), indicating that approximately 37.8% of patients with RVO are at risk of experiencing a CVA. Subgroup analysis shows consistent event rates for both BRVO (0.378; 95% CI: 0.372–0.384) and CRVO (0.378; 95% CI: 0.370–0.386), suggesting similar risks in both subgroups.

The studies by Chen et al. (2018), Wai et al. (2023), and Werther et al. (2011) are significant contributors to the pooled event rate, demonstrating narrow confidence intervals and precise estimates, which improve the reliability of the analysis. The absence of heterogeneity within subgroups ($I^2 = 0\%$ for both BRVO and CRVO) indicates consistent findings across studies.

Clinically, these results underscore the high risk of CVA in patients with RVO, regardless of the type (BRVO or CRVO). This highlights the importance of aggressive cardiovascular risk assessment and preventive strategies in these patients. Early intervention and long-term monitoring can reduce stroke risk and improve overall patient outcomes.

Sub-group analysis on the incidence of hemorrhagic CVA events based on type of RVO

The forest plot in Fig. 6 presents a subgroup meta-analysis on the incidence of hemorrhagic cerebrovascular accident (CVA) following retinal vein occlusion (RVO), with separate analyses for branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). The overall pooled event rate for hemorrhagic CVA across both subgroups is 0.327 (95% CI: 0.323–0.331), indicating that approximately 32.7% of patients with RVO experience hemorrhagic CVA.

Subgroup analysis reveals similar event rates for BRVO (0.325; 95% CI: 0.320–0.331) and CRVO (0.328; 95% CI: 0.322–0.334), with no significant heterogeneity within or between groups ($I^2 = 0\%$). The Chen et al. (2018) and Werther et al. (2011) studies are key contributors to these findings, offering precise estimates with narrow confidence intervals and significant weight in the analysis.

Clinically, these findings emphasize the high risk of hemorrhagic stroke in patients with RVO, regardless of the subtype (BRVO or CRVO). The consistency between subgroups highlights the need for comprehensive stroke prevention strategies in this population. Early identification of risk factors and the initiation of appropriate anticoagulation or blood pressure management are critical in reducing the incidence of hemorrhagic CVA and improving patient outcomes.

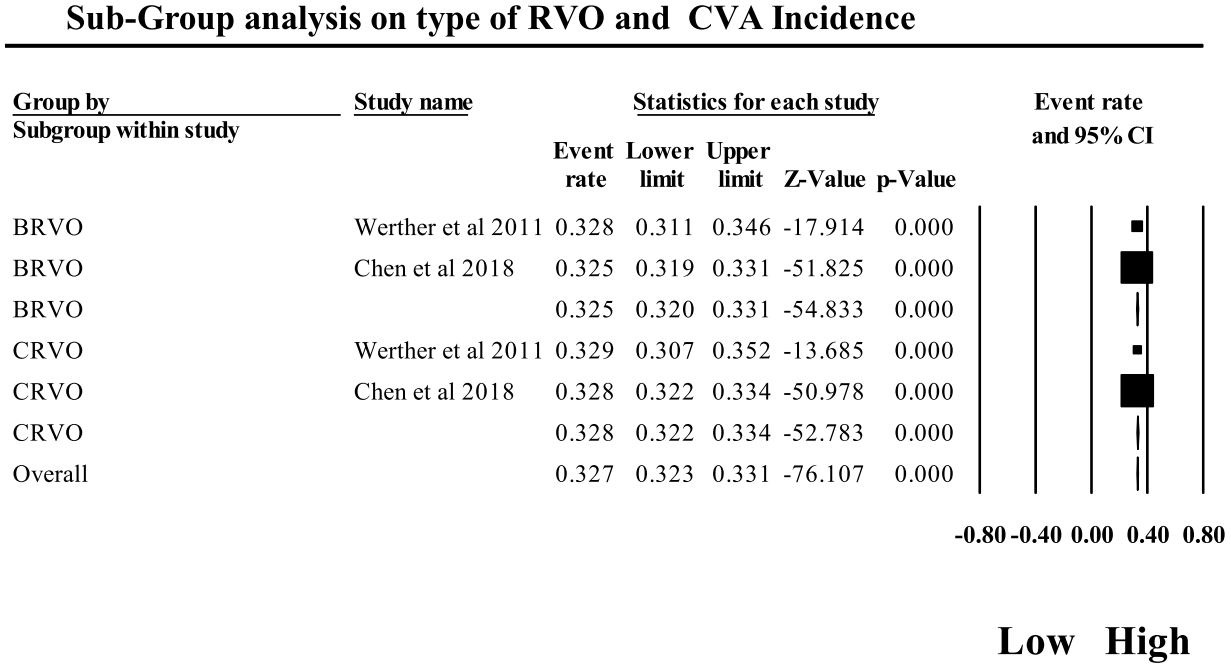

Fig. 6 Forest plots on sub-group analysis on the incidence of Hemorrhagic CVA events based on type of RVO

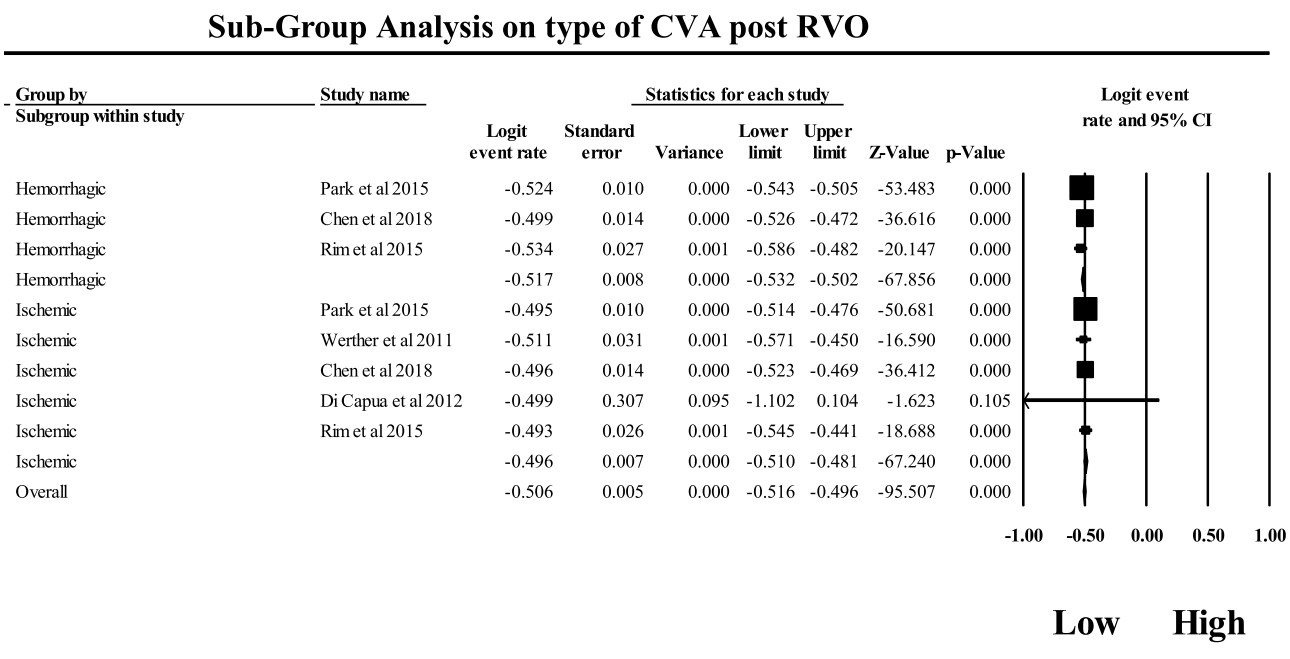

Fig. 7 Forest Plot on Sub-Group analysis on the type of CVA post RVO

Sub-group analysis on the type of cVA post RVO

The forest plot in Fig. 7 provides a subgroup analysis of the incidence of hemorrhagic and ischemic cerebrovascular accidents (CVA) following retinal vein occlusion (RVO). The overall logit event rate is −0.506 (95% CI: −0.516 to −0.496), which corresponds to an approximate raw event rate of 37%. This highlights that CVA is a relatively frequent complication in individuals with RVO.

The results are derived from a fixed-effect model with no significant heterogeneity across the included studies ($I^2 = 0\%$), indicating consistent findings across the population studied. The findings underline the need for clinical vigilance to identify and manage these complications early in RVO patients.

For hemorrhagic CVA, the subgroup analysis reveals a logit event rate of −0.517, which translates to an event rate of about 37.4%. Notable contributors to this subgroup include studies by Park et al. (2015) with a logit value of −0.524 and Chen et al. (2018) with a logit value of −0.499. Moderate heterogeneity ($I^2 = 25.93\%$) exists among the studies, suggesting some variability, potentially due to differences in population characteristics or study methodologies. Despite this, the findings remain clinically significant.

For ischemic CVA, the subgroup analysis shows a logit event rate of −0.496, corresponding to a raw event rate of 38.1%. Key contributors include Park et al. (2015) with a logit value of −0.495 and Chen et al. (2018) with a logit value of −0.496. This subgroup exhibits no heterogeneity ($I^2 = 0\%$), indicating consistent and robust results across the studies.

The findings of this analysis are clinically significant, as they emphasize a high risk of CVA, both ischemic and hemorrhagic, in patients with RVO. This necessitates proactive management of modifiable risk factors like hypertension, hyperlipidemia, and diabetes. Early detection and treatment of RVO are essential to minimize the risk of life-threatening complications, including CVA.

Mortality rate of CVO post RVO

The forest plot in Fig. 8 presents a meta-analysis on the mortality rate in patients with cerebrovascular accident (CVA) following retinal vein occlusion (RVO). The overall pooled event rate for mortality is 0.690 (95% CI: 0.684–0.695), indicating that approximately 69% of patients with CVA post-RVO experience mortality. The analysis includes six studies, all of which contribute significant weight to the overall estimate.

Ho et al. (2009) and Shih et al. (2015) are highly influential studies due to their large sample sizes and narrow confidence intervals, providing precise estimates with high consistency. The event rates in these studies (0.695 and 0.681, respectively) are close to the overall pooled estimate, reinforcing the robustness of the findings. Wai et al. (2023) and Bertelsen et al. (2014) also contribute prominently with event rates of 0.697 and 0.690, respectively.

The heterogeneity analysis shows a Q-value of 5.02 ($p = 0.41$) and $I^2 = 0\%$, indicating minimal variability between studies and justifying the use of a fixed-effect model.

The high mortality rate underscores the severity of CVA in patients with RVO, highlighting the need for aggressive management of cardiovascular risk factors.

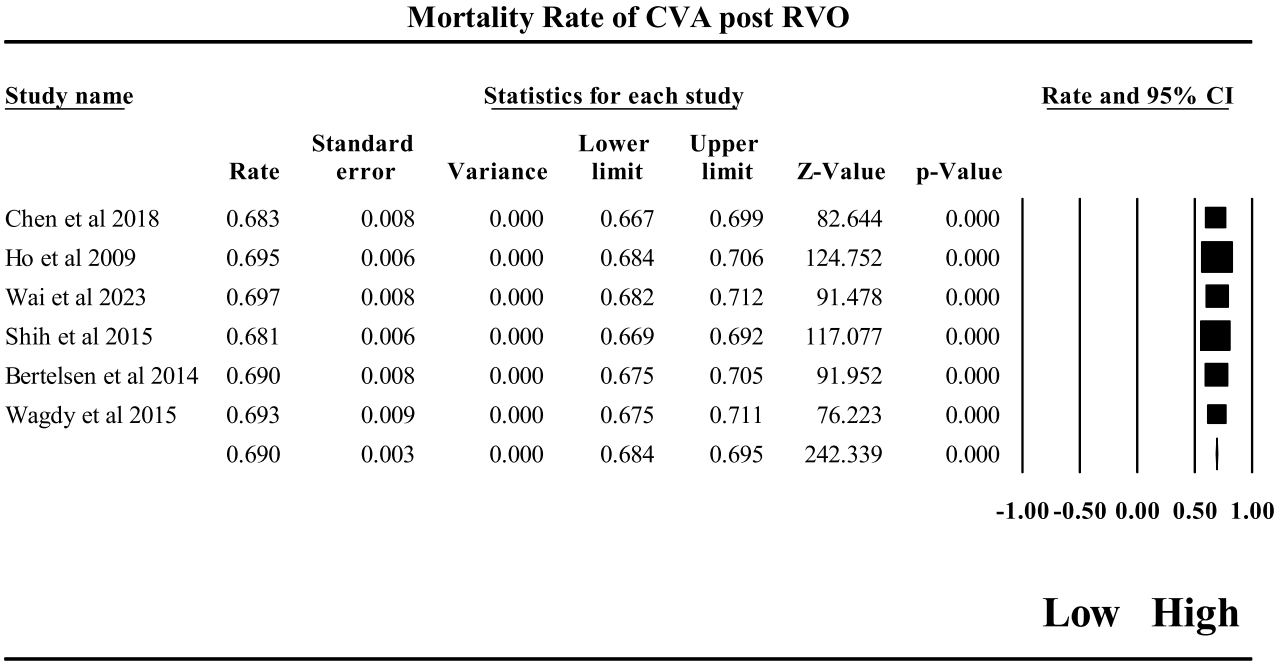

Fig. 8 Forest plot on mortality rate of CVA post RVA

Early intervention and post-stroke care are critical in reducing mortality and improving patient outcomes. These findings emphasize the importance of close monitoring and prevention strategies in high-risk populations.

Ischemic co-morbidities along with RVO

Incidence of ischemic cardiovascular events

The forest plot analysis in Fig. 9 provides valuable insights into the incidence of ischemic cardiac disease and cerebrovascular accidents (CVA) following retinal vein occlusion (RVO). The overall logit event rate is −1.692, which corresponds to a raw event rate of approximately 15.7%. This indicates a notable risk of ischemic events, such as ischemic heart disease and CVA, in patients with RVO. The analysis includes five studies, all of which contribute to this pooled estimate, with a fixed effect model showing no significant heterogeneity ($I^2 = 0\%$). This suggests a consistent pattern across the studies included in the analysis.

Key contributors to this analysis include Werther et al. (2011), which reports a logit event rate of −1.658, and Chen et al. (2018), with a logit value of −1.690. These studies provide robust evidence for the association between RVO and increased risk of ischemic cardiovascular events. Di Capua et al. (2012), with a logit value of −1.872, also contributes significantly, though it reports a higher level of variance, indicating some degree of heterogeneity. Despite the inclusion of studies with different variance levels, the fixed and random effects models converge to provide a consistent overall estimate.

Clinically, these results emphasize the need for proactive management of ischemic risks in RVO patients. Early identification of risk factors such as hypertension, diabetes, and atherosclerosis, along with aggressive cardiovascular monitoring, could help reduce the likelihood of ischemic events post-RVO, improving patient outcomes and reducing morbidity.

Incidence of DVT

The forest plot analysis for the incidence of deep vein thrombosis (DVT) and cerebrovascular accidents (CVA) post-retinal vein occlusion (RVO) in Fig. 10 presents a pooled logit event rate of −3.032. This logit value corresponds to a raw event rate of approximately 0.05%, which is relatively low, suggesting a modest incidence of both DVT and CVA in the studied cohort of RVO patients. The analysis includes two major studies: Wai et al. (2023) and Shih et al. (2015). Both studies contribute significantly to the analysis, with Wai et al. showing a logit event rate of −3.025, and Shih et al. contributing a rate of −3.054. Both studies have relatively tight confidence intervals, indicating consistent estimates across these studies.

The fixed-effect model for these studies demonstrates low heterogeneity ($I^2 = 0\%$), suggesting a consistent effect across the studies, with the pooled estimate being robust. The lack of significant variability is further confirmed by

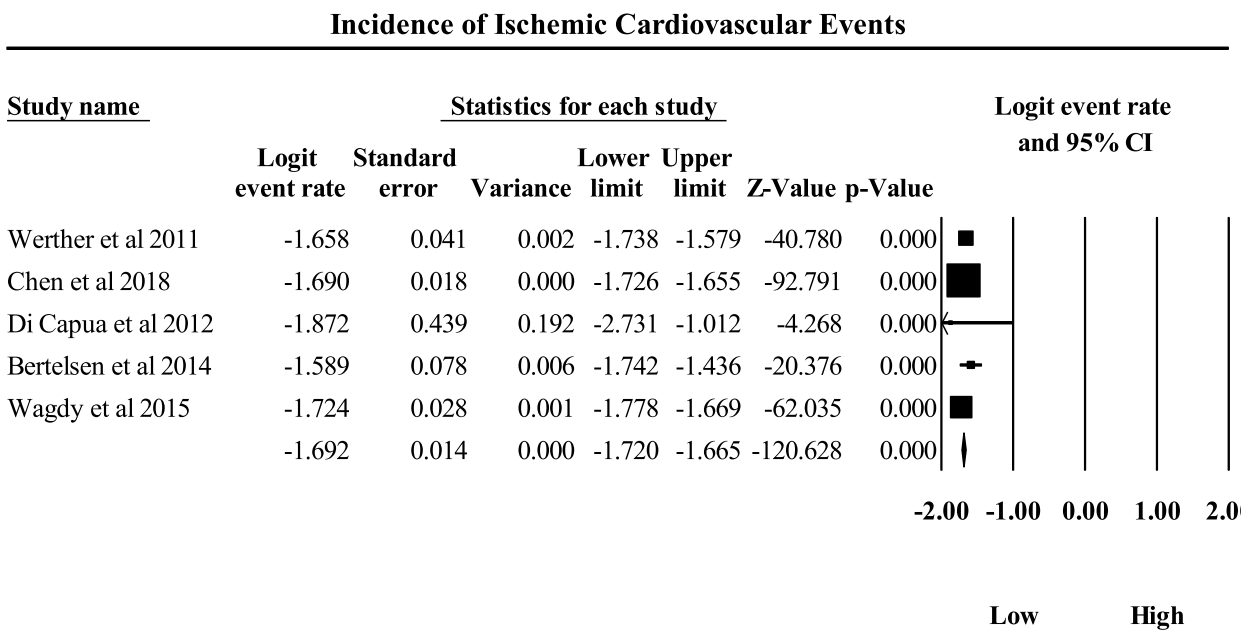

Fig. 9 Forest plot on Ischemic cardiovascular events along with CVA in RVO patients

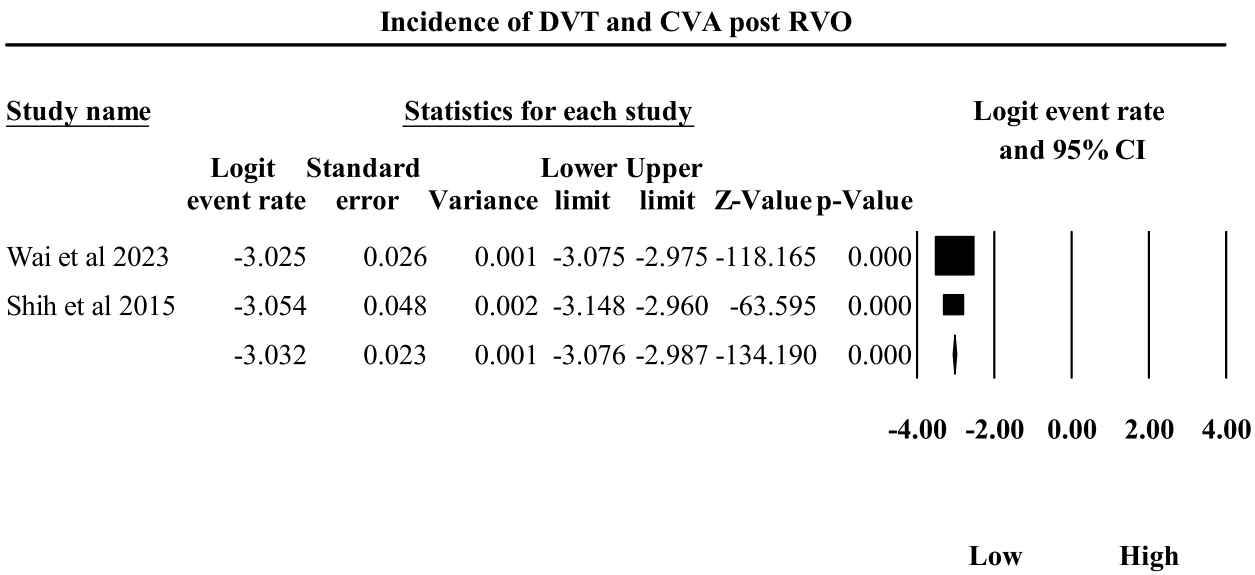

Fig. 10 Forest plot on incidence of DVT and CVA post RVO

the random-effects model, which also yields the same pooled estimate.

Clinically, the results highlight that while the combined incidence of DVT and CVA is low in post-RVO patients, it remains essential to monitor for these complications. Proactive management of thromboembolic risks, particularly in patients with additional cardiovascular or venous risk factors, is vital to minimizing morbidity and improving long-term outcomes.

Publication bias

The assessment of publication bias as depicted in Fig. 11 in the included meta-analyses involved both Begg's and Egger's tests across different outcomes. Begg's test, based on Kendall's tau, evaluates the correlation between study size and effect estimates. The results indicated no significant publication bias for most analyses, with Kendall's tau ranging from −0.321 to 0.190 across various outcomes. However, the test's limitations include low power in small

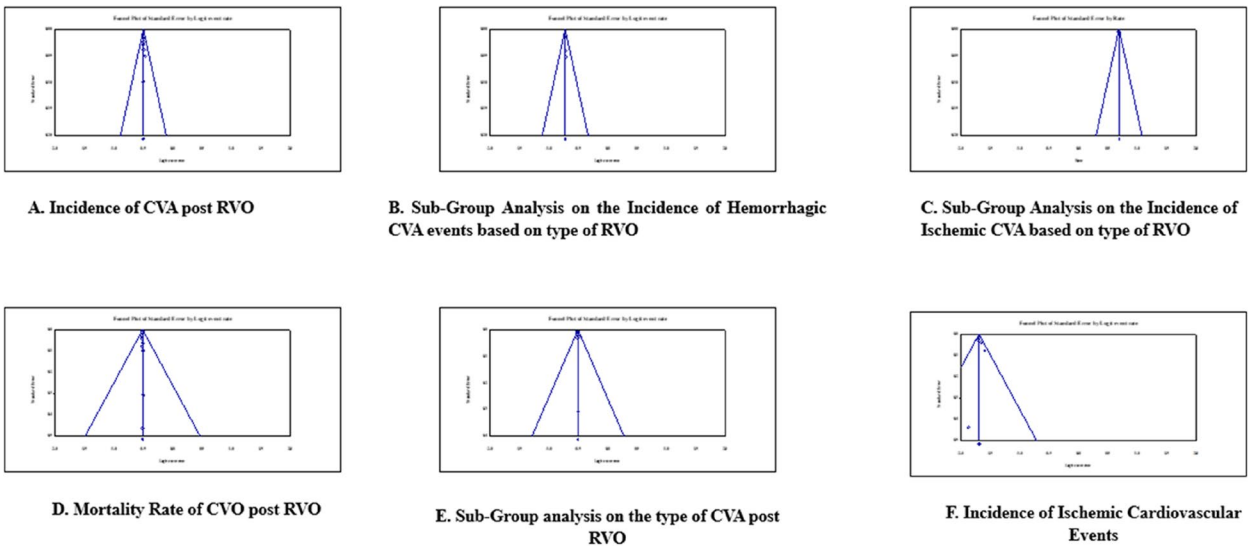

Fig. 11 Funnel Plots on Publication bias

meta-analyses, making non-significant results inconclusive. Egger's regression test, which detects asymmetry in funnel plots by assessing the intercept's deviation from zero, showed non-significant findings in most analyses, with p-values above 0.24 across all outcomes. The intercept values varied from −0.099 to 0.479, suggesting minimal small-study effects. The trim-and-fill method suggested a few missing studies in certain analyses but had little impact on pooled estimates, reinforcing the absence of strong publication bias. The fail-safe N analysis revealed many studies would be needed to nullify the observed effects, further indicating robust findings. In summary, both Begg's and Egger's tests suggest minimal publication bias, but caution is necessary due to the limited power of these methods in small sample sizes. While the trim-and-fill method identified potentially missing studies, the adjustments did not substantially alter the overall effect sizes, reinforcing confidence in the findings. Overall, the tests suggest minimal publication bias, but caution is warranted due to inherent limitations, necessitating visual funnel plot inspection, resulting in low intensity of bias.

Discussion

RVO is a common retinal vascular disease that occurs frequently in older adults and individuals with comorbid conditions like hypertension, diabetes, and hyperlipidemia. There is a significant overlap in the risk factors for RVO and cerebrovascular events because these disorders are known to predispose individuals to both of these conditions[32]. We conducted a comprehensive systematic review and meta-analysis to assess the impact of RVO on the incidence of CVA. This study synthesized data from multiple high-quality cohort and case–control studies to provide a robust estimate of the association between RVO and CVA risk. The findings revealed statistically significant evidence that RVO is positively associated with an increased risk of CVA, particularly in patients with a high cardiovascular risk profile. Our meta-analysis of the pooled data showed that those with RVO are significantly more likely to suffer from ischemic CVA [33], hemorrhagic CVA [20], transient ischemic attack (TIA) [23], and other cerebrovascular disorders [21].

This study's findings are supported by a related meta-analysis that was carried out in 2016 [1]. The 2016 study demonstrated that exposure to RVO was associated with an increased risk of CVA, particularly in individuals aged between 50 and 69 years. This previous research supports our current findings, demonstrating the connection between RVO and a higher risk of CVA. Both studies highlight the significance of RVO as a risk factor for CVA, particularly in middle-aged and older people. Another study conducted in 2016 provides additional data supporting the idea that RVO is associated with an increased risk of future cerebrovascular disease and myocardial infarction [34]. This study strengthens the current understanding of RVO as a significant predictor of not only CVA but also other serious cardiovascular events.

It was shown that people with RVO were more likely to experience an ischemic CVA, which happens when blood supply to the brain is obstructed. This result is consistent with the pathophysiological principles that induce RVO, wherein vascular occlusion and thrombus development in the retina may indicate a wider propensity for thromboembolic events in the systemic circulation [35]. Even though it is less frequent than ischemic CVA, hemorrhagic CVA has a strong correlation with RVO. This suggests that the retinal veins' vascular fragility and bleeding risk may similarly affect brain vasculature [36]. Age is a major factor in the incidence of RVO, especially beyond 50 years of age. This age-related increase in RVO prevalence adds to an increased risk of future CVA in older people [37].

Future research should focus on longitudinal cohort studies to establish causal relationships between RVO and cerebrovascular events. Investigating the genetic predisposition and inflammatory biomarkers associated with post-RVO strokes could provide personalized risk assessments and targeted interventions. Additionally, studies evaluating the efficacy of novel anticoagulation and antiplatelet strategies in RVO patients at high risk for stroke would be invaluable. Artificial intelligence (AI)-driven predictive models integrating fundus imaging, vascular health markers, and systemic risk factors could enhance early diagnosis and risk stratification for stroke prevention. Despite its robust methodology, this study has several limitations. First, the heterogeneity in study designs and population characteristics may have influenced the pooled estimates, although efforts were made to account for this via subgroup and meta-regression analyses. Second, the study primarily relies on observational data, which limits the ability to establish a direct causal relationship between RVO and CVA. Third, the lack of standardization in outcome definitions and follow-up durations across included studies introduces potential measurement bias. Additionally, while publication bias was assessed using Egger's and Begg's tests, the inclusion of predominantly English-language studies may have led to selection bias. Finally, there is limited data on the impact of specific interventions (e.g., anticoagulants, antihypertensives) on stroke risk in RVO patients, highlighting the need for prospective interventional trials. Addressing these limitations in future studies will be crucial for refining risk stratification and optimizing therapeutic strategies for patients with RVO at risk of stroke.

Conclusion

This meta-analysis provides compelling evidence linking retinal vein occlusion (RVO) to a significantly increased risk of cerebrovascular accidents (CVA) and mortality. The pooled event rate for CVA post-RVO was 37.5% (95% CI: 37.3%–37.8%), indicating that more than one in three patients with RVO are at risk of stroke. Subgroup analysis revealed comparable rates of ischemic (37.8%) and hemorrhagic (32.7%) CVA across both branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO), with no significant heterogeneity ($I^2 = 0\%$). These findings suggest that both forms of RVO are strong predictors of cerebrovascular risk. The high mortality rate of 69.0% (95% CI: 68.4%–69.5%) among RVO patients who develop CVA underscores the severity of these vascular events. Studies contributing to this estimate, such as those by Ho et al. (2009) and Shih et al. (2015), highlight the urgency of early intervention. Furthermore, RVO was associated with a 15.7% incidence of ischemic cardiovascular events ($I^2 = 0\%$), reinforcing the need for comprehensive cardiovascular risk management. While the incidence of deep vein thrombosis (DVT) post-RVO was relatively low at 0.05%, its occurrence warrants close monitoring, especially in high-risk populations.

Given these findings, aggressive risk factor modification is crucial. Proactive management of hypertension, diabetes, and dyslipidemia, coupled with regular cardiovascular screening, could significantly reduce stroke risk and improve survival outcomes in RVO patients. These results advocate for a multidisciplinary approach integrating ophthalmologists, neurologists, and cardiologists to ensure timely diagnosis, preventive strategies, and optimized treatment to mitigate RVO-related complications.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2

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We are keen to publish our work in BMC Ophthalmology, as we aim to contribute to the field of ophthalmology through high-quality and impactful research. We believe our findings will significantly enhance understanding and treatment of retinal vein occlusion.

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Authors' contributions

K.-Y. C. contributed to conceptualization, methodology, software, investigation, validation, writing the original draft, visualization, and formal analysis. H.-C. C. was responsible for conceptualization, methodology and software. C.-M. C. handled methodology, investigation, validation, supervision, and project administration. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable. This study does not involve human participants, human data or human tissue.

Consent for publication

Not applicable. This study does not involve individual data.

Competing interests

The authors declare no competing interests.

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