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# Long-term outcomes for patients treated for macular oedema secondary to retinal vein occlusion: a systematic review

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## ABSTRACT

This systematic review assessed the long-term outcomes for patients treated with intravitreal antivascular endothelial growth factor or dexamethasone for macular oedema (MO) secondary to retinal vein occlusion (RVO). Studies investigating patients of all ages with MO due to RVO only were included. The review was deliberately broad in scope, including comparative and non-comparative studies to ensure inclusion of real-world type evidence. Risk of bias was assessed. In total, 76 data sets were included (10 775 participants). Overall, mean best-corrected visual acuity (BCVA) improved from baseline to 5 years by 16.1 letters (p<0.01). BCVA improved from baseline in both central RVO (CRVO) and branch RVO (BRVOs) at 2 years, by 9.1 (p<0.01) (difference from baseline in CRVOs) and 9.1 (p<0.01) letters, respectively. At 5 years, BCVA improved from baseline in CRVOs by 15.6 letters and in BRVOs by 16.2; the difference between RVO types was not significant (p=0.18). Two studies had 5-year data for ranibizumab, and improvement was evident. There was no significant difference between outcomes in randomised controlled trials (RCTs) compared with non RCTs. These results suggest a benefit to receiving long-term intravitreal treatments for MO due to RVO.

## INTRODUCTION

Retinal vein occlusion (RVO) is the second most common retinal cause of vision loss after diabetic retinopathy. In 2019, global prevalence of RVO was estimated to be 0.77% in adults aged 30–89 years.[1] RVO is caused by thrombus formation, thought to occur due to compression from an adjacent arteriosclerotic artery, where artery and vein cross and share a common adventitial sheath.[2] Central RVO (CRVO) has been associated with a significantly lower quality of life has been reported.[3] Macular oedema (MO) affects 75% of patients with branch RVO (BRVO) and 85% patients with CRVO in England and Wales[2] and is the most common cause of visual loss in RVO. MO secondary to RVO is thought to occur due to increased hydrostatic pressure, inflammatory cytokines and increased capillary permeability causing leakage into the extracellular space.[4] Vascular endothelial growth factor (VEGF) is a key cytokine mediating capillary leakage and subsequent MO and is therefore targeted by several intravitreal therapies (bevacizumab, ranibizumab and aflibercept). Dexamethasone is also used as an intravitreal treatment.[2]

Although the outcomes of these treatments are well described in the literature, their efficacy after two or more years of use is less well established. Landmark studies have had outcomes at 52 weeks (BRAVO), 24 (VIBRANT),[5 6] 52 (CRUISE),[7] 100 (COPERNICUS),[8] 76 (GALILEO)[8] and 24 (GENEVA)[9] weeks. Anecdotally, patients want to know longer-term outcomes and an evidence based, comprehensive answer is lacking. This systematic review aimed to evaluate treatment outcomes assessed after 2 years or more of intravitreal injection for patients with MO caused by RVO.

## METHODS

This was a systematic review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used to guide the conduct and report of this review.[10]

The aim was to investigate the long-term outcomes for patients with MO due to RVO, treated with intravitreal injections of (1) anti-VEGFs, specifically aflibercept, bevacizumab or ranibizumab or (2) the dexamethasone implant or (3) any combination of these, described as 'combination treatment' throughout. Long term was defined as outcomes assessed at 2–5 years. It was planned to accept comparative and non-comparative studies and retrospective and prospective studies. Studies including using laser treatment as the comparator arm were excluded. The outcomes of interest were best-corrected visual acuity (BCVA) and central retinal thickness (CRT) in µm.

An electronic search was conducted in the Medline, Embase, Cochrane and Web of Science databases to identify potentially eligible publications. Search filters were English language studies only, and no time

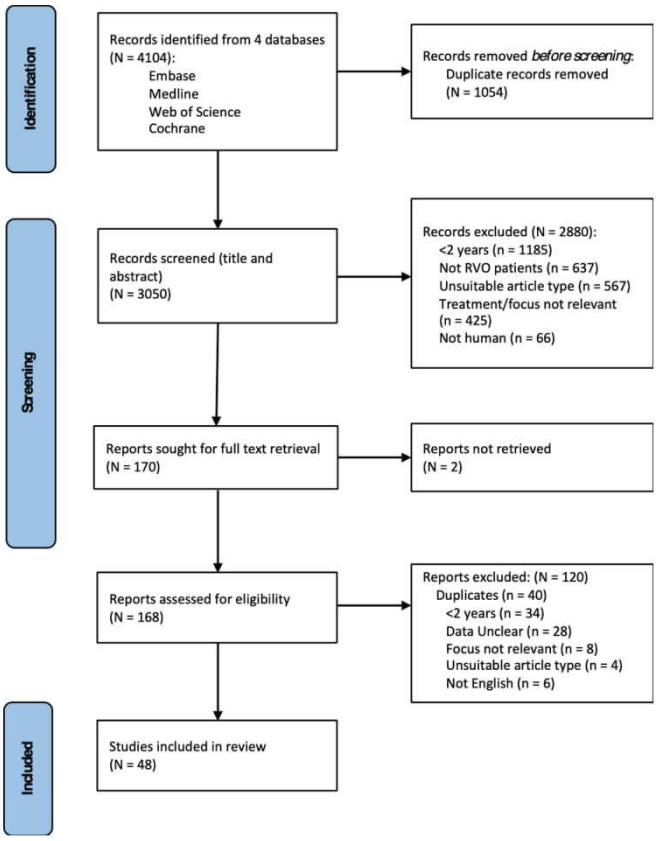


**Figure 1** Flow chart of selection and screening process. Adapted from Page et al.[10]

limits were set on publication dates. The search strategy used is summarised in online supplemental tables 1, 2.

After application of the search term a list of 'potentially eligible studies' resulted. One reviewer (AH) screened each title and abstract. If eligibility was unclear, studies were included at this stage. Duplicates were identified and the resulting papers were examined again to produce a list of 'definitely eligible' studies. This list was used for data extraction. Variables extracted were patient age (mean, median and range), the percentage male, country of study and ethnicity of participants if given, study design, RVO type and drug used. Although there is no generally accepted consensus on whether hemiretinal and hemispheric vein occlusions (HRVOs) are comparable to CRVO or BRVOs, for this study HRVOs were grouped with CRVOs, given the clinical implications of involvement of half the retina, that is, the likely poorer prognosis than with involvement of a single quadrant or less. If more than one drug was given to a patient, this was classified as 'combination treatment'. Baseline BCVA and CRT were recorded at baseline and if available at 2 years, 3 years, 4 years and 5 years after initiation of treatment. Any BCVA values recorded in the log(MAR) scale or Snellen chart were converted to Early Treatment Diabetic Retinopathy Study (ETDRS) letters. The study-level risk of bias was assessed using the Cochrane Risk of Bias Tool[11] for RCTs, the Critical Appraisal Skills Programme cohort checklist[12] for cohort studies, and the Joanna Briggs Institute Critical Appraisal case series checklist[13] for retrospective studies. Studies included were categorised into low risk, high risk or unclear categories based on selection, detection, attrition and reporting bias domains.[14] If information needed to judge the risk of bias was lacking, studies were classified as 'unclear risk of bias'.

Data were analysed using SPSS V.27. The mean, SD, range and 95% CIs were compared at each year of follow-up with baseline for BCVA and CRT for all papers and for each RVO type, treatment used and study type (divided into RCTs and 'other' study types). The means for BCVA and CRT were compared at each time point using independent samples t-test for comparing two groups (for example RCT vs non-RCT study types) and one-way analysis of variance (ANOVA) test for comparing greater than two groups (drug type). The significance value was set at $p<0.05$.

## RESULTS

There were 4104 potentially eligible studies (figure 1). After elimination of duplicates, 3050 studies were left, which were screened using the title and abstracts. In total, 2880 studies were excluded at this stage; 38.9% had a follow-up time less than 2 years, including studies with a 2-year mean follow-up but range starting less than 2 years. Then 170 studies were left to screen using full text if available: two studies had no full text available. A further 120 were excluded for reasons which included the follow-up time totalling less than 2 years, absolute BCVA or CRT values not given, or full text not available in English. Overall, 48 studies were eligible for analysis (online supplemental table 3). Studies were classified as 'CRVO', 'BRVO' or 'mixed RVO type'. If articles investigated patients with CRVO and BRVO and presented separate outcomes by RVO type, the studies' cohorts were analysed separately based on RVO type; thus, there were 76 cohorts in total from 48 studies. Eight studies included both RVO types, however, did not present data separately; therefore, these were recorded as one cohort and classified as 'mixed' RVO type'. Eight studies separated RVO type into ischaemic and non-ischaemic,[15] however, due to the small numbers and inconsistent definitions, ischaemic status was not recorded. Three studies were deemed to have a high risk of bias and 11 studies had moderate risk of bias (online supplemental tables 4, 5).

The 76 cohorts with BCVA at baseline constituted 10 775 participants. At 2 years, there were data for 65 cohorts (10 304 participants), at 3 years 25 cohorts (5775 participants), at 4 years 11 cohorts (501 participants) and at 5 years, 8 cohorts (402 participants) (online supplemental table 6).

For CRVOs, the mean baseline BCVA was 48.2 (95% CI 44.0 to 52.4) letters and for BRVOs 55.4 (95% CI 51.7 to 59.1) letters. After 2 years, BCVA improved in CRVOs by 9.1 letters and in BRVOs also by 9.1 letters, to 57.3 (95% CI 51.9 to 62.7, $p<0.01$) and 64.5 (95% CI 58.2 to 70.7, $p<0.01$) letters, respectively. After 3 years BCVA declined

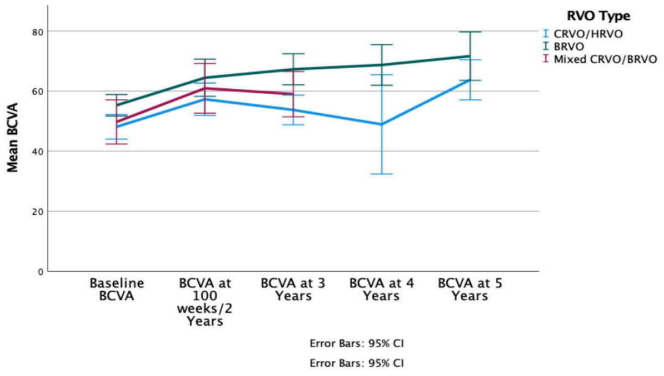


**Figure 2** Mean BCVA from baseline to 5 years after initial treatment for each RVO type. BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CRVO central retinal vein occlusion; HRVO, hemiretinal and hemispheric vein occlusion; RVO, retinal vein occlusion.

for CRVOs to 53.7 (95% CI 48.4 to 59.1, p<0.01) letters and improved from baseline for BRVOs to 67.3 (95% CI 61.4 to 73.1, p<0.01) letters. BCVA improved from baseline at 5 years for CRVOs by 15.6 letters to 63.8 (95% CI 53.3 to 74.2, p<0.01) letters and for BRVOs by 16.2 to 71.6 (95% CI: 59.0 to 84.3, p=0.01) letters, respectively (figure 2).

Mean baseline CRT was 603.1 µm (95% CI 560.4 to 645.8) for CRVOs and 496.7 µm (95% CI 464.6 to 528.8) for BRVOs. For all patients, regardless of RVO type, mean CRT decreased from 554.3 µm (95% CI 527.1 to 581.6) to 314.4 µm (95% CI 299.2 to 329.7) (p<0.01 vs baseline) after 2 years. At 5 years follow-up, the mean decrease in CRT for CRVOs was 254.2 µm (p=0.01) and 147.8 µm for BRVOs (p=0.02) (figure 3).

When drugs were compared (figure 4) mean baseline BCVA was lowest in patients who received combination treatment during the study (49.1 letters, 95% CI 44.8 to 53.4), however, this improved to 56.9 (95% CI 51.7 to 62.2, p<0.01 difference from baseline) letters and 69.7 (95% CI 61.2 to 78.2, p=0.01 difference from baseline)

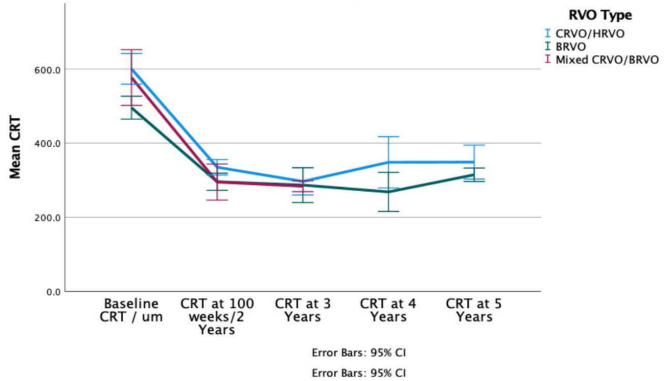


**Figure 3** Mean central retinal thickness (CRT) from baseline to 5 years after initial treatment for each RVO type. BRVO, branch retinal vein occlusion; CRVO central retinal vein occlusion; HRVO, hemiretinal and hemispheric vein occlusion; RVO, retinal vein occlusion.

letters after 2 and 5 years, respectively. Not all treatment types had follow-up periods beyond 2 years. Ranibizumab had 28 cohorts at baseline (2262 participants) and 8 cohorts (280 participants) with data at 3 years. BCVA for ranibizumab improved 11.2 letters from 53.4 at baseline to 3 years (95% CI 49.1 to 57.6, p<0.01). Dexamethasone had 8 cohorts at baseline with 1165 participants and 5 cohorts (703 participants) at 3 years. BCVA for dexamethasone improved 6.3 letters from 50.1 at baseline at 3 years (95% CI 41.6 to 58.6, p=0.55). Bevacizumab had 8 cohorts at baseline with 582 participants and 1 cohort (57 participants) at 3 years. BCVA with bevacizumab decreased by 2.5 letters from 55.1 letters baseline at 3 years (95% CI 40.7 to 69.2) to 52.6 at 3 years. Two of the studies with 'ranibizumab only' cohorts had 5-year follow-up: mean BCVA decreased from 3 years to 61.8 (95% CI 19.2 to 104.3) letters (p=0.077), though this still was an improvement from baseline.

There were 30 retrospective case series, 28 prospective cohort studies, 15 RCTs and 3 prospective case series. When comparing study types, studies were categorised into two groups, RCTs and non-RCTs. At 4 years (there was no 5-year data available for RCTs) in RCTs, BCVA improved by 13.6 letters from 55.5 letters (95% CI 52.1 to 58.9) at baseline to 69.1 letters (95% CI 4.9 to 133, p=0.11) compared with a 10-letter improvement in non-RCTs from 50.6 letters at baseline (95% CI 47.5 to 53.8) to 60.6 (95% CI 48.9 to 72.2, p<0.01) (figure 5). The CRT results similarly varied between RCT and non-RCT studies. At 4 years, in RCTs, there was a decrease in CRT of 366 µm, from 570.7 µm (95% CI 472.4 to 668.9) at baseline to 204.7 µm (95% CI 1.9 to 407.3, p=0.13), and in non-RCTs, CRT decreased by 196.8 µm from 549.6 µm (95% CI 525.7 to 573.5) at baseline to 352.8 µm (95% CI 293.2 to 412.5, p<0.01).

The heterogeneity of studies led to varied study characteristics. Thirty-three studies followed patients for up to 2 years whereas others had up to 5 years' follow-up. Studies varied according to the data source used, for example, most retrospective studies reviewed electronic medical records,[16] whereas in RCTs and prospective cohort studies data were recorded contemporaneously.[17] Twenty-six studies included only treatment naïve patients. Whereas in six studies, although baseline BCVA prior to original treatment was not recorded, patients with previous treatment for MO due to RVO were not excluded.[18] Some studies gave a baseline BCVA and CRT measurement for inclusion.[18 19] Ten studies gave separate data for both CRVOs and BRVOs[20] and 10 had CRVO data only,[21] while 12 had BRVO data only.[22] The remaining six studies either combined data or didn't specify RVO type, and therefore, were assumed to contain both CRVO and BRVO patients.[23] Studies varied on use of equipment to measure CRT. Nineteen studies used the Heidelberg Spectralis OCT machine.[24] Thirteen studies used the Cirrus HD-OCT, Carl Zeiss Meditec OCT machine[25] and two used the 3D-OCT 2000 OCT machine.[26 27] The other studies did not specify what equipment was used.

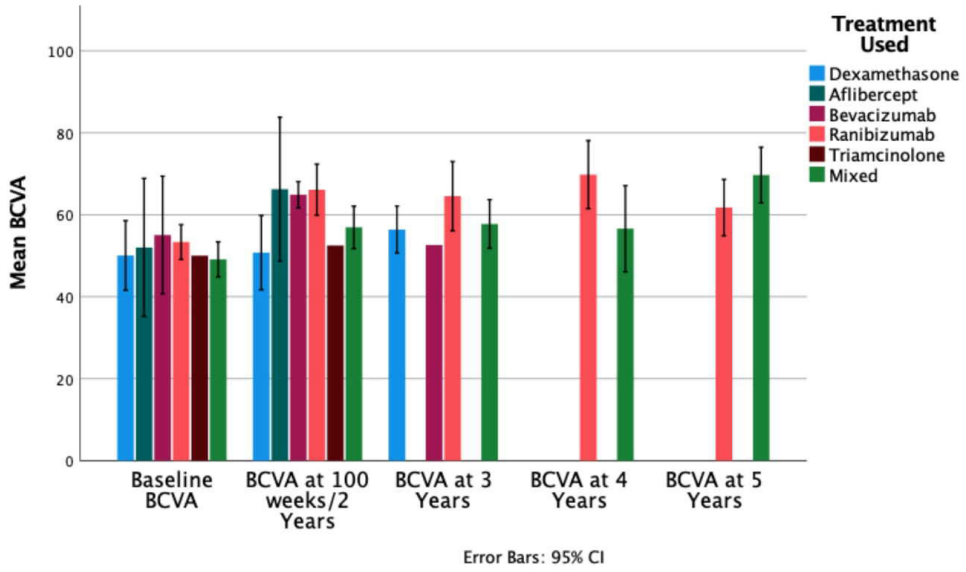


**Figure 4** Mean BCVA at each timepoint according to treatment type. BCVA, best-corrected visual acuity.

One RCT randomised patients to receive a certain drug against sham[28]; the outcomes for patients in the sham arm were disregarded. Three RCTs randomised patients to receive different doses of the same drug,[29] which were recorded as one drug type, and three randomised patients into different treatment groups and results were recorded separately for the purposes of our study.[20]

## DISCUSSION

This systematic review revealed clinically meaningful improvement in BCVA and CRT for up to 5 years for patients treated with intravitreal anti-VEGF or dexamethasone for MO secondary to RVO. It was deliberately the case that data were synthesised from disparate studies, so while formal meta-analysis would have been inappropriate, our review gives a picture of long-term outcomes, combining clinical trial and real-world settings.

Overall, mean BCVA improved from baseline up to 5 years by 16.1 ETDRS letters. At 5 years, BCVA improved from 48.2 letters at baseline to 63.8 in CRVOs and from 55.4 letters to 71.7 letters in BRVOs. CRT decreased by 254.2 µm from 603.1 µm at baseline in CRVOs, and by 181.9 µm from 496.7 µm at baseline in BRVOs. Thus, patients can be encouraged that sustained benefits are possible up to at least 5 years with ongoing treatment. At 5 years, though BCVA and CRT were better for BRVOs than CRVOs, there was no significant difference between CRVO and BRVO patients in BCVA (p=0.18) or CRT (p=0.23), but this may be due to smaller numbers followed up for this long.

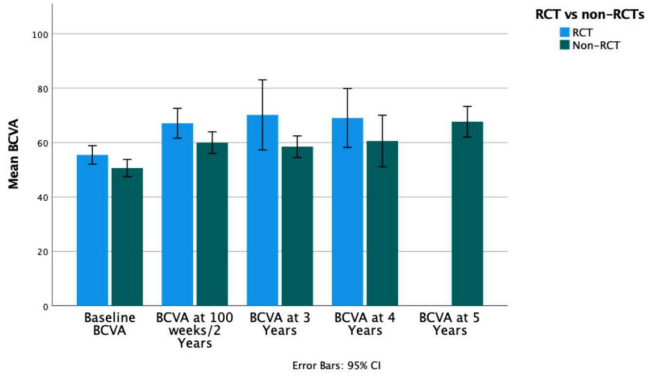


**Figure 5** Bar graph comparing mean BCVA in RCT against non-RCT studies at each time point. BCVA, best-corrected visual acuity. RCT, randomised controlled trials.

The inclusion criteria were set to include various study designs. RCTs are the gold standard, with guaranteed scheduled visits, and strict eligibility criteria, often excluding patients with poor baseline vision or comorbidities. RCTs might be expected to provide potentially better results than real-world studies.[30] However, in this review, there was no significant difference between BCVA and CRT results at 4 years between RCTs and non-RCTs. Injection frequency was rarely and inconsistently reported, and so was not analysed in this review. Although biases may have been a factor, for example, in selection of participants into non controlled prospective studies that outcomes in non-RCTs were as good as those in RCTs may give encouragement to those managing RVOs in the 'real world'.

The study numbers for aflibercept and bevacizumab were too small to draw any meaningful conclusions. For the 28 studies and 2262 participants with 'ranibizumab only cohorts', BCVA improved from 53.4 letters at baseline to 61.8 after 5 years (2 cohorts with 21 participants at 5 years). For dexamethasone implant only cohorts, BCVA improved from baseline to 3 years by 6.3 letters to 56.4 letters. Repeated steroid injections will cause cataract,[31] which may have blunted absolute BCVA results. For patients treated with a combination treatment, the necessity to switch patients from one drug to another probably resulted from a suboptimal response with the

original drug, and so a poorer prognosis may have been expected in this cohort, perhaps reflected in the lower baseline BCVA for combination treatment, though BCVA improved in a clinically meaningful way up to 5 years.

Intravitreal anti-VEGF injections have been proven to be effective and are used first line in treating MO secondary to other diseases including diabetic MO (DMO).[32 33] The Protocol T Extension study[34] was an RCT investigating long term outcomes of patients with MO secondary to DMO treated with either aflibercept, bevacizumab or ranibizumab over 5 years. BCVA improved from baseline after 5 years, though had fallen from year 2 to 5. Studies and reviews cannot be compared, especially across indications: all that can be said is that sustained improvements have been demonstrated with DMO too, though reasons for the fall after year 2 warrant consideration.

The strengths of this review included the broad inclusion criteria. This review aimed to capture the totality of evidence, including real-world practice as represented, in many cases, by retrospective and prospective uncontrolled studies. Analysing according to type of RVO, drug used and study type (RCT and non-RCT) was informative: although no formal analysis was performed on the interaction of these categories, the likelihood of interaction and confounding of results in clinical practice is low.

In this review, studies had various primary outcomes and methods to measure BCVA and CRT results. For example, some recorded percentage of patients with an improvement in BCVA of 15 letters or greater, while other studies presented absolute values or graphs only. Indeed, data was lost due to the exclusion of 27 studies which included data which was either unclear, in the form of graphs or only provided change in BCVA or CRT rather than absolute values.

Long-term prospective studies are needed to investigate patient outcomes beyond the first few years of treatment. Furthermore, it is important to consider the impact these treatments have on patients: only one study presented QoL data.[15] Also, studies investigating the long-term cost-effectiveness of intravitreal anti-VEGF or steroid therapy, balanced with the long-term benefits to patients should be conducted. This systematic review provides evidence of long-term benefits of treatment for patients with MO due to both CRVO and BRVO.

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**Contributors** MW conceived the idea, guided the review method and supervised its conduct. He checked and interpreted the analysis and edited the manuscript. AH conducted the search, screened and selected papers, conducted data extraction and analysis and performed statistical analysis.

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Supplemental Table 1. Search concepts for search one.

| | Population$_1$ | Population$_2$ | Intervention |
|---|---|---|---|
| *OR* | Macular oedema | Retina* vein occlusion | Intravitreal injection* |
| *OR* | Macular edema | Retinal vein blockage | Intravitreal treatment* |
| *OR* | | Retinal venous occlusion | Intravitreal drug administration |
| *OR* | | Retinal venous blockage | Intravitreal |
| | | Retinal disease* | |
| | *AND* | *AND* | *AND* |

Supplemental Table 2. Additional search concepts for search two.

| | Intervention |
|---|---|
| *OR* | Bevacizumab |
| *OR* | Aflibercept |
| *OR* | Ranibizumab |
| *OR* | Dexamethasone |
| *OR* | Triamcinolone |
| *OR* | Steroid |
| | *AND* |

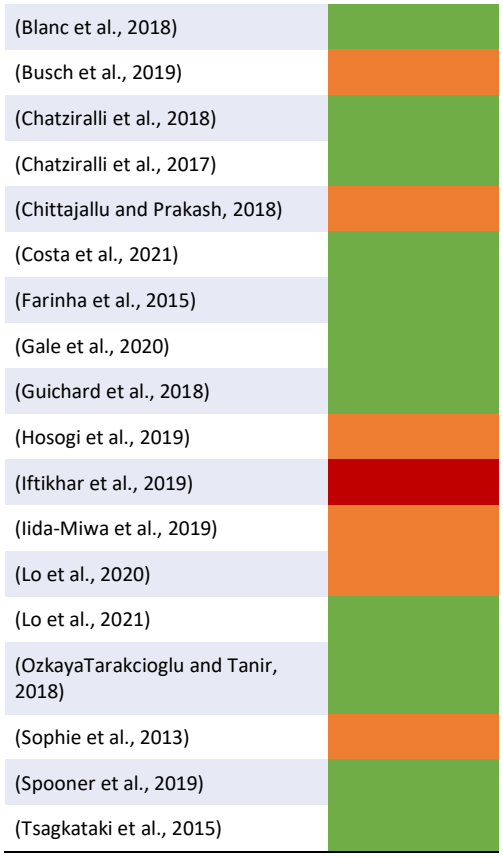
Supplemental Table 3. Included papers in this review (n=48)

| Study author & year | Participants (n) | Study type | RVO type | Drug regimen | Study outcomes | Conclusions |
|---|---|---|---|---|---|---|
| (Abdallah et al., 2019) | 9 | Retrospective case series | Separate CRVO & BRVO data | Dexamethasone | BCVA & CRT at 3 years | No significant vision gains with dexamethasone. |
| (Bajric & Bakri, 2016) | 5 | Retrospective case series | CRVO only | Combination | BCVA & CRT at 2, 3 & 4 years | BCVA & CRT improvement maintained at four years. |
| (Blanc et al., 2018) | 66 | Retrospective case series | Mixed | Dexamethasone & combination | BCVA & CRT at 2 & 3 years | Dexamethasone effective at 3 years. |
| (Blin et al., 2018) | 301 | Cohort | Separate CRVO & BRVO data | Ranibizumab | BCVA & CRT at 2 years | Ranibizumab effective at 2 years. |
| (Brown et al., 2014) | 15 | Cohort | CRVO only | Ranibizumab | BCVA & CRT at 2 years | Ranibizumab improved vision. |
| (Busch et al., 2019) | 155 | Retrospective case series | Separate CRVO & BRVO data | Combination | BCVA & CRT at 2 & 3 years | Early treatment improved final outcomes. |
| (Calugaru & Calugaru, 2015) | 57 | Cohort | CRVO only | Bevacizumab | BCVA & CRT at 3 years | Bevacizumab improved vision at 3 years. |
| (Campochiaro et al., 2010a) | 40 | RCT | Separate CRVO & BRVO data | Combination | BCVA & CRT at 2 years | Long term visual improvement with anti-VEGF. |
| (Campochiaro et al., 2014) | 66 | Cohort | Separate CRVO & BRVO data | Ranibizumab | BCVA & CRT at 2, 3 & 4 years | Ranibizumab improves long term visual outcomes. |
| (Chatziralli et al., 2017) | 15 | Retrospective case series | CRVO only | Combination | BCVA & CRT at 2 years | Anti-VEGF is effective for MO due to RVO. |
| (Chatziralli et al., 2018) | 54 | Retrospective case series | Separate CRVO & BRVO data | Ranibizumab | BCVA & CRT at 2, 3 & 4 years | Ranibizumab is effective long term. |
| (Chittajallu & Prakash, 2018) | 101 | Retrospective case series | BRVO only | Ranibizumab | BCVA at 2 years | Long term ranibizumab is effective. |
| (Costa et al., 2021) | 208 | Retrospective case series | Mixed | Dexamethasone & combination | BCVA & CRT at 3 years | Intravitreal treatment improved long term outcomes. |
| (Farinha et al., 2015) | 32 | Retrospective case series | Separate CRVO & BRVO data | Ranibizumab | BCVA & CRT at 2 & 3 years | Ranibizumab was satisfactory long term. |
| (Gale et al., 2020) | 4879 | Retrospective case series | CRVO only | Ranibizumab, dexamethasone & combination | BCVA at 2 & 3 years | Better visual outcomes with ranibizumab than other treatments. |
| (Guichard et al., 2018) | 76 | Retrospective case series | Mixed | Ranibizumab | BCVA & CRT at 2 years | Treat & extend superior to PRN for MO due to RVO. |
| (Heier et al., 2012) | 203 | RCT | Separate CRVO & BRVO data | Ranibizumab | BCVA & CRT at 2 years | Ranibizumab is safe & effective. |
| (Heier et al., 2014) | 114 | RCT | CRVO only | Aflibercept | BCVA & CRT at 2 years | Anatomical improvements reduced between weeks 52 & 100. |
| (Hikichi et al., 2014) | 89 | Cohort | BRVO only | Bevacizumab | BCVA & CRT at 2 years | Bevacizumab is beneficial at 2 years |
| (Horner et al., 2020) | 54 | Cohort | Separate CRVO & BRVO data | Ranibizumab & combination | BCVA & CRT at 2 & 3 years | Combination therapy effective for MO due to RVO. |
| (Hosogi et al., 2019) | 32 | Retrospective case series | BRVO only | Ranibizumab | BCVA & CRT at 2 years | Ranibizumab effective for BRVO patients. |
| (Hykin et al., 2019) | 463 | RCT | CRVO only | Ranibizumab, aflibercept & bevacizumab | BCVA & CRT at 2 years | Aflibercept was non-inferior to ranibizumab. |
| (Iftikhar et al., 2019) | 90 | Prospective case series | Separate CRVO & BRVO data | Combination | BCVA & CRT at 2, 3, 4 & 5 years | Sustained anti-VEGF improved visual & anatomical outcomes. |
| (Inagaki et al., 2019) | 20 | Cohort | BRVO only | Ranibizumab | BCVA & CRT at 2 years | Ranibizumab improved vision at 2 years. |

| Study author & year | Participants (n) | Study type | RVO type | Drug regimen | Study outcomes | Conclusions |
|---|---|---|---|---|---|---|
| (Khurana et al., 2019) | 16 | Cohort | CRVO only | Aflibercept | BCVA & CRT at 2 years | Aflibercept provided improvement at 2 years |
| (Korobelnik et al., 2016) | 375 | Cohort | Separate CRVO & BRVO data | Dexamethasone | BCVA & CRT at 2 years | Dexamethasone implant is safe |
| (Larsen et al., 2018) | 357 | Cohort | CRVO only | Ranibizumab | BCVA & CRT at 2 years | Ranibizumab is effective at 2 years |
| (Lee, Jung & Sohn, 2014) | 453 | Cohort | BRVO only | Triamcinolone, bevacizumab & combination | BCVA at 2 years | Anti-VEGF provides improved BCVA at 2 years. |
| (Lida-Miwa et al., 2019) | 58 | Prospective case series | BRVO only | Ranibizumab | BCVA & CRT at 2 years | Neovascular changes present in BRVO treated with ranibizumab. |
| (Lo et al., 2020) | 214 | Retrospective case series | Mixed | Combination | BCVA & CRT at 2 years | Early BCVA & CRT improvements may predict long-term outcomes. |
| (Lo et al., 2021) | 214 | Retrospective case series | Separate CRVO & BRVO data | Combination | BCVA & CRT at 2 years | Early anatomic response increases chance of treatment cessation. |
| (Loukiano et al., 2016) | 33 | Cohort | Separate CRVO & BRVO data | Bevacizumab | BCVA & CRT at 2 years | Bevacizumab provides long term BCVA improvement. |
| (Maggio et al., 2020) | 223 | Cohort | Separate CRVO & BRVO data | Combination | BCVA & CRT at 2, 3, 4 & 5 years | Ranibizumab & dexamethasone effective long term. |
| (Mansour et al., 2018) | 10 | Cohort | Mixed | Aflibercept | BCVA at 2 years | BCVA improves over 2 years with aflibercept. |
| (McAllister et al., 2018) | 29 | RCT | CRVO only | Ranibizumab | BCVA & CRT at 2 years | Ranibizumab effective in CRVO patients. |
| (Ozkaya, Tarakcioglu & Tanir, 2018) | 174 | Retrospective case series | BRVO only | Ranibizumab & dexamethasone | BCVA & CRT at 2 years | Ranibizumab & dexamethasone effective in BRVO. |
| (Risard et al., 2011) | 20 | Cohort | CRVO only | Ranibizumab | BCVA & CRT at 2 years | Ranibizumab improves visual & anatomical outcomes. |
| (Sakanishi et al., 2021) | 40 | Cohort | BRVO only | Aflibercept | BCVA & CRT at 2 years | Aflibercept effective at 2 years for BRVO . |
| (Scott et al., 2011) | 389 | RCT | Separate CRVO & BRVO data | Combination | BCVA & CRT at 2 years | Younger age predictive of higher BCVA. |
| (Sen et al., 2021) | 267 | RCT | CRVO only | Combination | BCVA at 2 years | HIgher baseline BCVA was predictive of better BCVA outcomes. |
| (Sophie et al., 2013) | 21 | Retrospective case series | Separate CRVO & BRVO data | Ranibizumab | BCVA at 2 years | Infrequent ranibizumab not sufficient to treat MO due to RVO. |
| (Sophie et al., 2019) | 205 | RCT | BRVO only | Ranibizumab | BCVA & CRT at 2 years | Perfusion maintenance crucial for good outcomes in CRVO. |
| (Spooner et al., 2019) | 68 | Retrospective case series | Separate CRVO & BRVO data | Combination | BCVA & CRT at 5 years | Anti-VEGF achieved good long term outcomes for RVO. |
| (Stredova et al., 2019) | 39 | Cohort | BRVO only | Ranibizumab | BCVA & CRT at 2 years | Ranibizumab improved long term outcomes for BRVO. |
| (Tadayoni et al., 2017) | 183 | RCT | BRVO only | Ranibizumab | BCVA & CRT at 2 years | Long term efficacy & safety of ranibizumab proven. |
| (Tsagkataki et al., 2015) | 35 | Retrospective case series | BRVO only | Bevacizumab | BCVA & CRT at 2 years | Bevacizumab provided resolution of MO in one third of patients. |
| (Volkmann et al., 2020) | 16 | Cohort | Mixed | Combination | BCVA at 2 years | BCVA improves with anti-VEGF. |
| (Wu et al., 2009) | 63 | Cohort | BRVO only | Bevacizumab | BCVA & CRT at 2 years | Bevacizumab is effective at 2 years. |

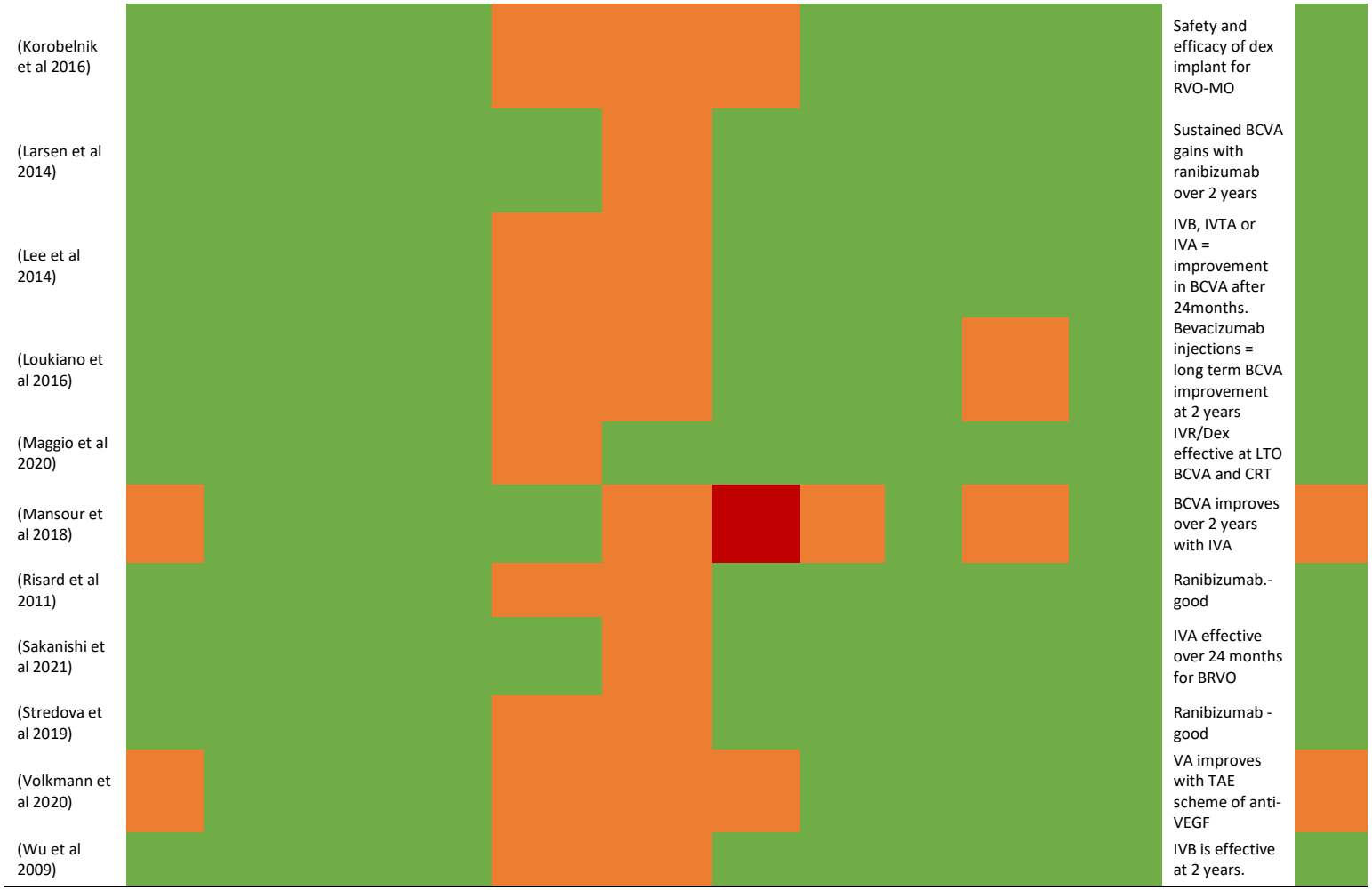
Supplemental Table 4. Overall Risk of Bias for RCTs, Cohort Studies and Case Series.

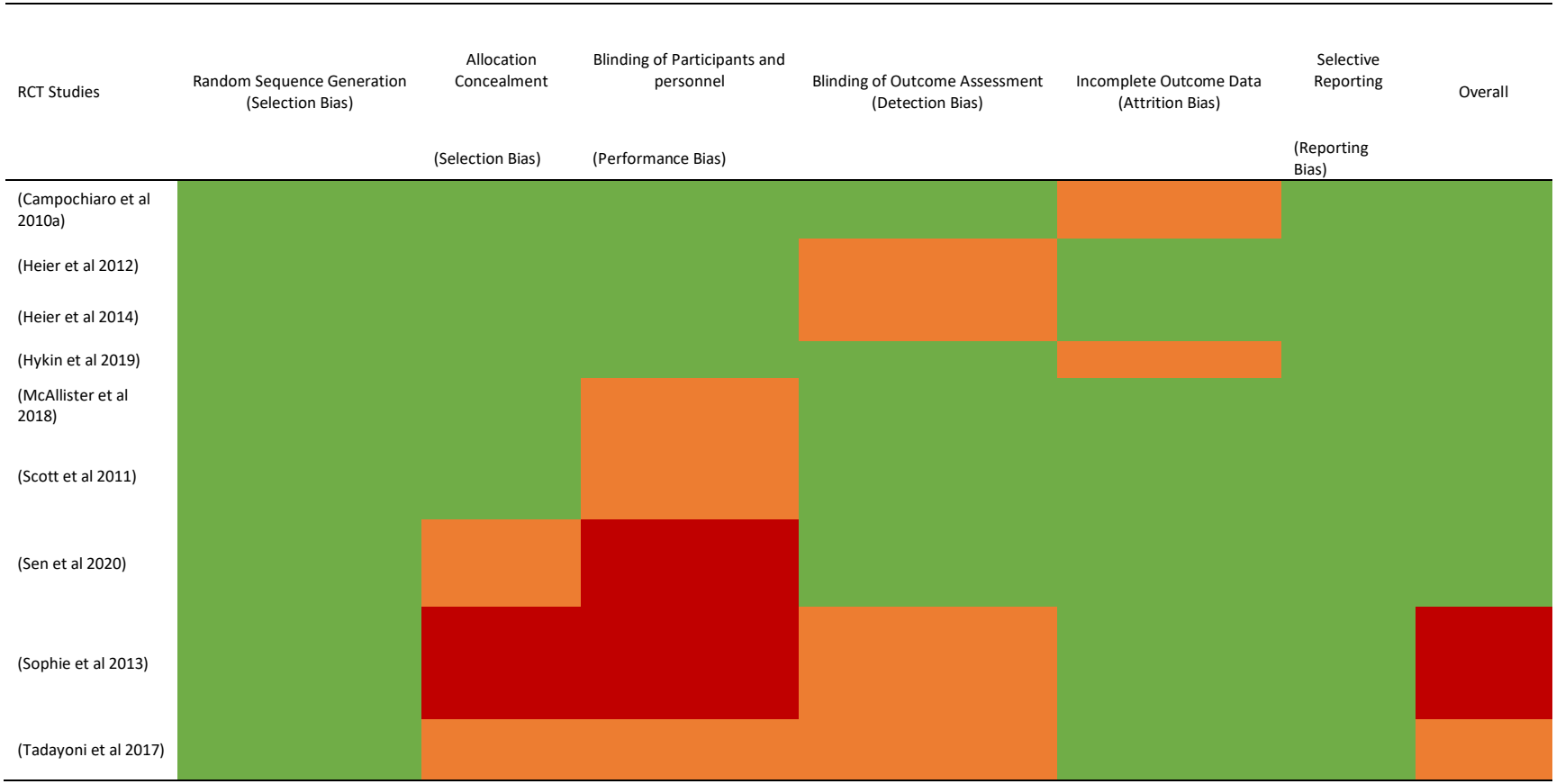
| RCT - Cochrane Risk of Bias Tool | Overall Risk of Bias |
|---|---|
| (Campochiaro et al., 2010a) | |
| (Heier et al., 2012) | |
| (Heier et al., 2014) | |
| (Hykin et al., 2019) | |
| (McAllister et al., 2018) | |
| (Scott et al., 2011) | |
| (Sen et al., 2021) | |
| (Sophie et al., 2019) | |
| (Tadayoni et al., 2017) | |
| Cohort Studies - CASP Tool | |
| (Blin et al., 2018) | |
| (Brown et al., 2014) | |
| (Calugaru and Calugaru, 2015) | |
| (Campochiaro et al., 2014) | |
| (Hikichi et al., 2014) | |
| (Horner et al., 2020) | |
| (Inagaki et al., 2019) | |
| (Khurana et al., 2019) | |
| (Korobelnik et al., 2016) | |
| (Larsen et al., 2018) | |
| (LeeJung and Sohn, 2014) | |
| (Loukianou et al., 2016) | |
| (Maggio et al., 2020) | |
| (Mansour et al., 2018) | |
| (Risard et al., 2011) | |
| (Sakanishi et al., 2021) | |
| (Stredova et al., 2019) | |
| (Volkmann et al., 2020) | |
| (Wu et al., 2009) | |
| Case Series - JBI Tool | |
| (Abdallah et al., 2019) | |
| (Bajric and Bakri, 2016) | |

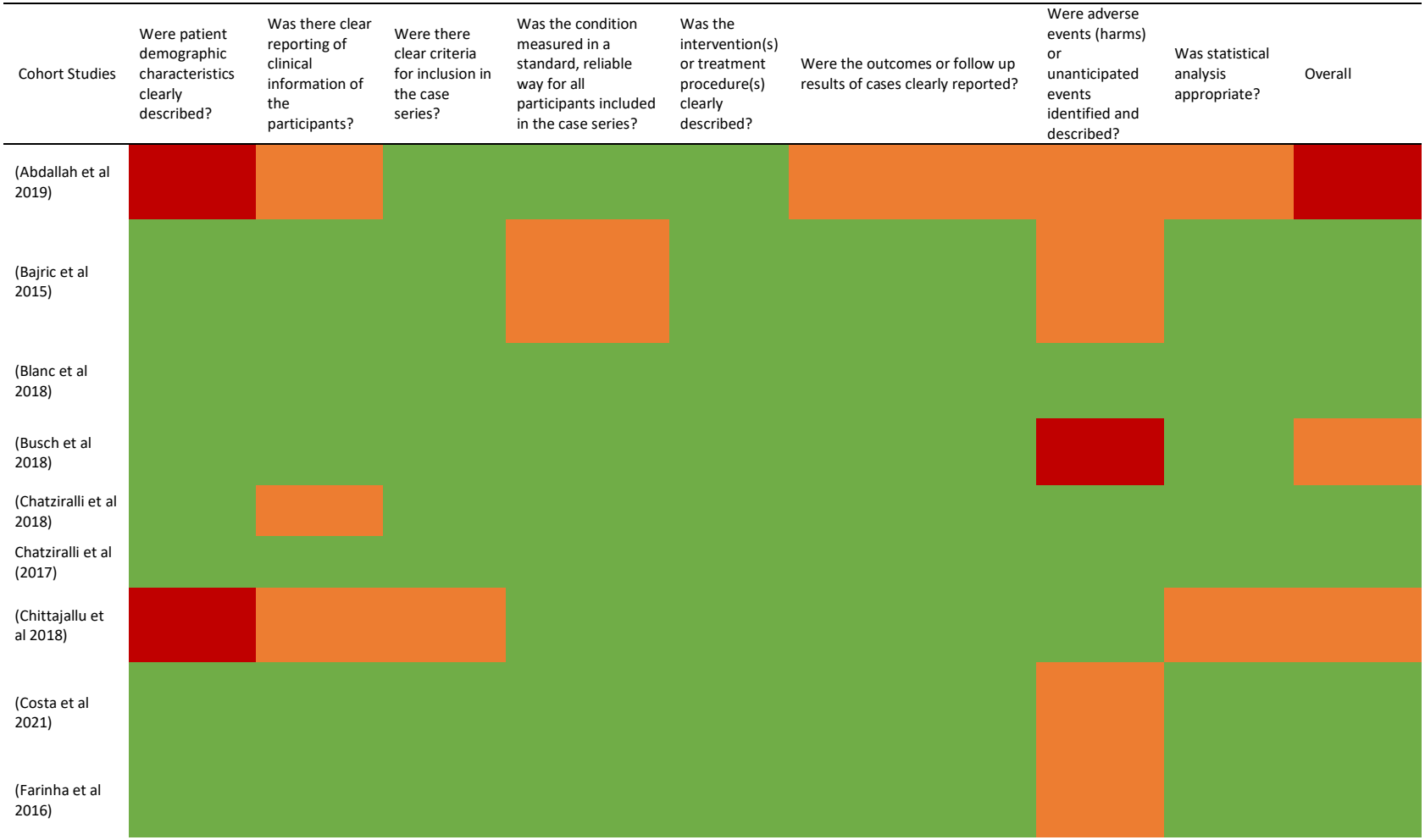

(Blanc et al., 2018)
(Busch et al., 2019)
(Chatziralli et al., 2018)
(Chatziralli et al., 2017)
(Chittajallu and Prakash, 2018)
(Costa et al., 2021)
(Farinha et al., 2015)
(Gale et al., 2020)
(Guichard et al., 2018)
(Hosogi et al., 2019)
(Iftikhar et al., 2019)
(Iida-Miwa et al., 2019)
(Lo et al., 2020)
(Lo et al., 2021)
(OzkayaTarakcioglu and Tanir, 2018)
(Sophie et al., 2013)
(Spooner et al., 2019)
(Tsagkataki et al., 2015)

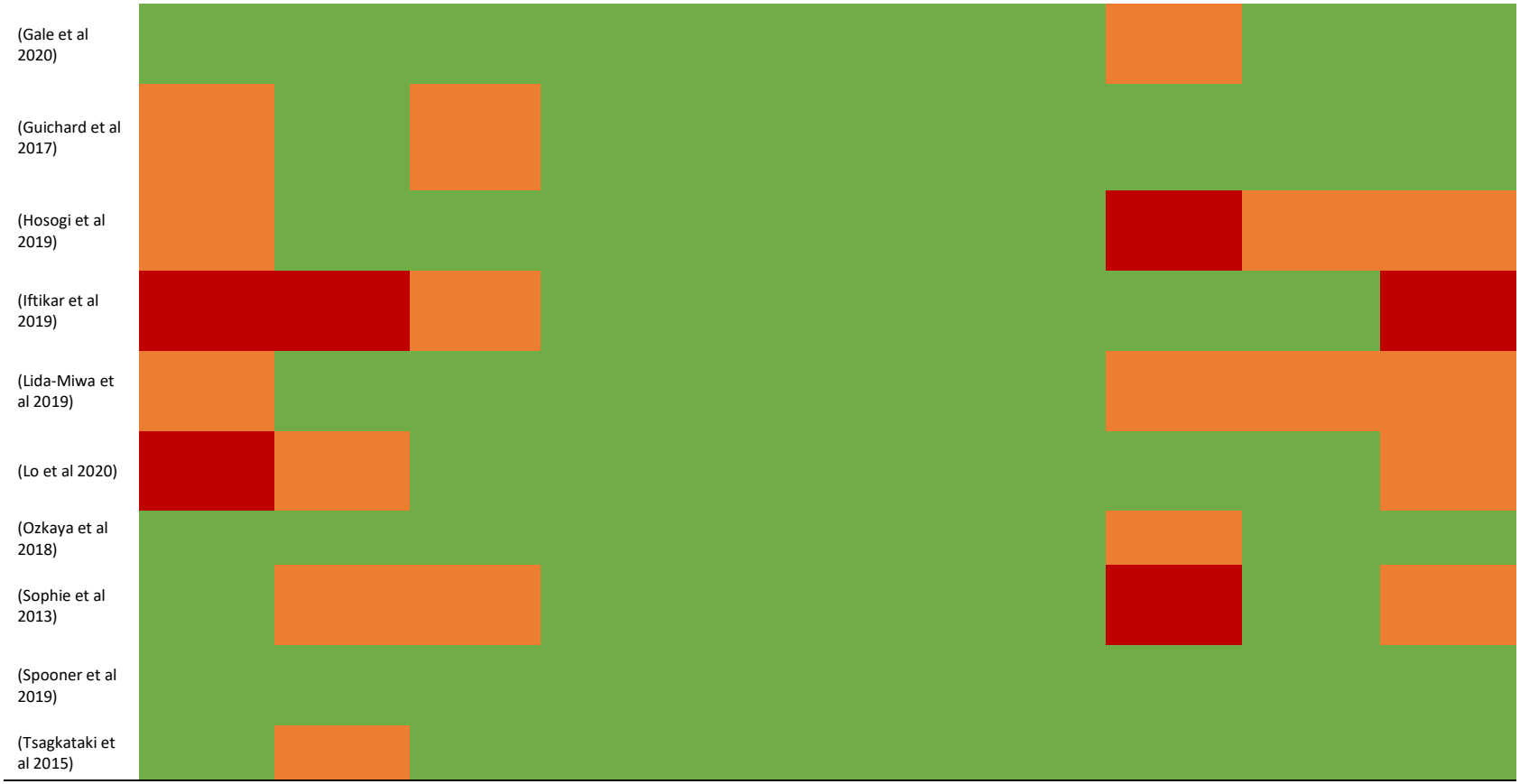
Supplemental Table 5 – Risk of Bias Tables

| Case Series | Did the study address a clearly focused issue? | Was the cohort recruited in an acceptable way? | Was the exposure accurately measured to minimise bias? | Was the outcome accurately measured to minimise bias? | Have the authors identified all important confounding factors? | Have they taken account of the confounding factors in the design and/or analysis? | Was the follow up of subjects complete enough? | Was the follow up of subjects long enough? | Do you believe the results? | 10. Can the results be applied to the local population? | 11. Do the results of this study fit with other available evidence? | 12. What are the implications of this study for practice? | Overall |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Blin et al 2018) | | | | | | | | | | | | Long term use of ranibizumab is effective. | |
| (Brown et al 2014) | | | | | | | | | | | | Ranibizumab in CRVO improvesretinal anatomy and vision | |
| (Calugaru and Calugaru 2015) | | | | | | | | | | | | "IVB = sustained vision over 3 years" | |
| (Campochiaro et al 2014) | | | | | | | | | | | | "LTO with ranibizumab are excellent' | |
| (Hikichi et al 2014) | | | | | | | | | | | | IVB is beneficial over 2 years | |
| (Horner et al 2020) | | | | | | | | | | | | Combination therapy is effective | |
| Inagaki et al 2019) | | | | | | | | | | | | "IVR + PRN gave pretty good visual outcome at month 24" | |
| (Khurana et al 2019) | | | | | | | | | | | | Sustained benefits of TAE aflibercept over 2 years | |


(Korobelnik et al 2016)
Safety and efficacy of dex implant for RVO-MO
(Larsen et al 2014)
Sustained BCVA gains with ranibizumab over 2 years
(Lee et al 2014)
IVB, IVTA or IVA = improvement in BCVA after 24months.
(Loukiano et al 2016)
Bevacizumab injections = long term BCVA improvement at 2 years
(Maggio et al 2020)
IVR/Dex effective at LTO BCVA and CRT
(Mansour et al 2018)
BCVA improves over 2 years with IVA
(Risard et al 2011)
Ranibizumab.- good
(Sakanishi et al 2021)
IVA effective over 24 months for BRVO
(Stredova et al 2019)
Ranibizumab - good
(Volkmann et al 2020)
VA improves with TAE scheme of anti-VEGF
(Wu et al 2009)
IVB is effective at 2 years.


RCT Studies
Random Sequence Generation (Selection Bias)
Allocation Concealment (Selection Bias)
Blinding of Participants and personnel (Performance Bias)
Blinding of Outcome Assessment (Detection Bias)
Incomplete Outcome Data (Attrition Bias)
Selective Reporting (Reporting Bias)
Overall
(Campochiaro et al 2010a)
(Heier et al 2012)
(Heier et al 2014)
(Hykin et al 2019)
(McAllister et al 2018)
(Scott et al 2011)
(Sen et al 2020)
(Sophie et al 2013)
(Tadayoni et al 2017)


Cohort Studies
Were patient demographic characteristics clearly described?
Was there clear reporting of clinical information of the participants?
Were there clear criteria for inclusion in the case series?
Was the condition measured in a standard, reliable way for all participants included in the case series?
Was the intervention(s) or treatment procedure(s) clearly described?
Were the outcomes or follow up results of cases clearly reported?
Were adverse events (harms) or unanticipated events identified and described?
Was statistical analysis appropriate?
Overall
(Abdallah et al 2019)
(Bajric et al 2015)
(Blanc et al 2018)
(Busch et al 2018)
(Chatziralli et al 2018)
Chatziralli et al (2017)
(Chittajallu et al 2018)
(Costa et al 2021)
(Farinha et al 2016)


(Gale et al 2020)
(Guichard et al 2017)
(Hosogi et al 2019)
(Iftikar et al 2019)
(Lida-Miwa et al 2019)
(Lo et al 2020)
(Ozkaya et al 2018)
(Sophie et al 2013)
(Spooner et al 2019)
(Tsagkataki et al 2015)

Supplemental Table 6. Total number of studies and participants with data for BCVA and CRT for each year of follow up.

| | No. Studies | No. Participants |
|---|---|---|
| Baseline BCVA: | 76 | 10775 |
| BCVA at 2 years: | 65 | 10304 |
| BCVA at 3 years: | 25 | 5775 |
| BCVA at 4 years: | 11 | 501 |
| BCVA at 5 years: | 8 | 402 |

| | No. Studies | No. Participants |
|---|---|---|
| Baseline CRT: | 69 | 5486 |
| CRT at 2 years: | 57 | 4887 |
| CRT at 3 years: | 21 | 912 |
| CRT at 4 years: | 11 | 501 |
| CRT at 5 years: | 6 | 381 |

## PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | ✓ |
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | ✓ |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | ✓ |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | ✓ |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | ✓ |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | ✓ |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | ✓ |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | ✓ |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | ✓ |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | ✓ |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | ✓ |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | ✓ |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | ✓ |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | ✓ |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | ✓ |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | ✓ |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | ✓ |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | ✓ |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | ✓ |

## PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **RESULTS** | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | ✓ |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | ✓ |
| Study characteristics | 17 | Cite each included study and present its characteristics. | ✓ |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | ✓ |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | ✓ |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | ✓ |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | ✓ |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | ✓ |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | ✓ |
| **DISCUSSION** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | ✓ |
| | 23b | Discuss any limitations of the evidence included in the review. | ✓ |
| | 23c | Discuss any limitations of the review processes used. | ✓ |
| | 23d | Discuss implications of the results for practice, policy, and future research. | ✓ |
| **OTHER INFORMATION** | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | ✓ |
| Competing interests | 26 | Declare any competing interests of review authors. | ✓ |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | ✓ |

*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/