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The Association of Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio with Retinal Vein Occlusion: A Systematic Review and Meta-Analysis

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Structured Abstract

Purpose:

The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are emerging haematological inflammatory biomarkers. However, their significance in retinal vein occlusion (RVO) and its subtypes, branch and central RVO (BRVO and CRVO, respectively), is uncertain. This systematic review and meta-analysis aimed to clarify the association of NLR and PLR with RVO.

Methods:

We searched MEDLINE (Ovid), Embase (Ovid), and the Cochrane Library for studies investigating the association of NLR and PLR with RVO from inception to 2 December 2020. We used random-effects inverse-variance modelling to generate pooled effect measures. We used bivariate Bayesian modelling to meta-analyse the ability of NLR and PLR to differ between individuals with and without RVO, and performed meta-regression and sensitivity analyses to explore inter-study heterogeneity.

Results:

Eight studies published encompassing 1,059 patients were included for analysis. Both NLR and PLR were significantly elevated in RVO, with pooled mean differences of 0.63 (95% confidence interval (CI) 0.31–0.95) and 21.49 (95% CI 10.03–32.95) respectively. The pooled sensitivity, specificity, and area under the Bayesian summary receiver operating characteristic curve were, respectively, 0.629 (95% credible interval (CrI) 0.284–0.872), 0.731 (95% CrI 0.373–0.934) and 0.688 (95% CrI 0.358–0.872) for NLR; and 0.645 (95% CrI 0.456–0.779), 0.616 (95% CrI 0.428–0.761) and 0.621 (95% CrI 0.452–

0.741) for PLR. Mean and variability of age and diabetes mellitus prevalence partially explained between-study heterogeneity.

Conclusions:
NLR and PLR are significantly elevated in RVO. Future research is needed to investigate the potential prognostic value and independence of these findings.

Key Words
neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, retinal vein occlusion, systematic review and meta-analysis

Introduction
With an estimated international prevalence of 16 million affected individuals, retinal vein occlusion (RVO) is the second most common cause of vision loss due to retinal vascular disease after diabetic retinopathy, and is an important cause of visual loss in older adults (Rogers et al. 2010). RVO can be subdivided into branch and central RVO (BRVO and CRVO respectively), where BRVO occurs due to distal venous obstruction resulting in localised haemorrhage, while CRVO occurs with obstruction at the lamina cribrosa leading to extensive retinal involvement. Depending on clinical features and the degree of retinal capillary nonperfusion on fluorescein angiography, CRVO can be further subcategorised into ischaemic and non-ischaemic variants. While visual complications can be more severe in CRVO, its prevalence worldwide (0.08%) is less than that of BRVO (0.44%) (Rogers et al. 2010).

The natural history of RVO is variable depending on the its subtype, extent of occlusion, severity of initial visual defect, and development of complications which can include macular oedema, neovascularisation, vitreous haemorrhage, and neovascular glaucoma (Finkelstein 1992; 1997). Patients with BRVO without macular oedema are frequently asymptomatic and do not experience deterioration in best corrected visual acuity (BCVA), while those with macular oedema may experience spontaneous improvement in BCVA within the first 3 months, as demonstrated by the Branch Retinal Vein Occlusion Study (1984). For those who did not improve to 20/40 or better by 3 months post, 34% experienced improvement by 3 years and 23% deteriorated to 20/200 or worse, with an average BCVA of 20/70 (1984). Patients with CRVO generally experience worse outcomes than BRVO. The Central Retinal Vein Occlusion Study (1997) found that two thirds of those who

presented with BCVA 20/40 or better maintained this BCVA at 3 years, while 10% worsened beyond 20/200. Nearly half of those who presented with BCVA between 20/50 and 20/200 were likely to maintain this, though one third worsened beyond 20/200. Only a fifth of those who presented with BCVA worse than 20/200 experienced some improvement in acuity. Notably, a systematic review found that average initial BCVA for ischaemic CRVO was worse than 20/200, with further deterioration over time (McIntosh et al. 2010).

The pathophysiology of RVO is incompletely understood. However, BRVO is thought to result from mechanical compression of retinal venules at arteriovenous crossings by thickened atherosclerotic arterioles within a common adventitial sheath, with secondary changes including endothelial loss, turbulent blood flow, and thrombosis (Zhao et al. 1993). CRVO is thought to be the product of thrombosis in the central retinal vein secondary to atherosclerotic central retinal artery changes and compression at crossing points within a common sheath at or posterior to the lamina cribosa (Green et al. 1981). The most significant RVO risk factors appear to be increasing age and hypertension (Rogers et al. 2010; Bertelsen et al. 2012; Newman-Casey et al. 2014). Other systemic risk factors include atherosclerotic risk factors (dyslipidaemia, diabetes, smoking, obesity, and cardiovascular disease) (O'Mahoney et al. 2008) and thrombophilia (Janssen et al. 2005). Additionally, the presence of ocular risk factors such as retinal arteriolar abnormalities and glaucoma further increase the risk of a RVO (Sivaprasad et al. 2015). Interestingly, RVO has also been found to be a marker of underlying cardiovascular disease, with associations with future stroke and cardiovascular mortality found in observational studies (Cugati et al. 2007; Werther et al. 2011).

Both atherosclerosis and thrombosis predispose to RVO, and all three conditions are associated with underlying inflammation (Tousoulis et al. 2003; Deobhakta & Chang 2013). The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are emerging inflammatory biomarkers that have been widely investigated across multiple disciplines, including retinal disease (Walsh et al. 2005; Papa et al. 2008; Tokgoz et al. 2013; Ulu et al. 2013). However, the significance of NLR and PLR in RVO is uncertain. Clarifying the relationship between NLR, PLR, and RVO may advance our understanding of the underlying pathophysiology and may lead to additional insights on risk stratification, severity assessment, prognostication and clinical management of this potentially blinding condition.

Hence, we performed a systematic review and meta-analysis to investigate the association of NLR and PLR with RVO. We additionally discuss gaps in the literature, and offer possible future directions in this research space.

Methods

Study Design and Registration

This systematic review and meta-analysis of case-control studies synthesised study-level data. We prospectively registered protocol details with PROSPERO (CRD42020221189, registered 17 December 2020), and there were no major protocol deviations. Reporting complied with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al. 2000).

Eligibility Criteria for Considering Studies for This Review

We included original human studies reporting haematological measurements of NLR and PLR grouped by RVO status. BRVO was defined as retinal haemorrhage in the wedge-shaped distribution of an affected retinal vein on fundus examination with variable retinal oedema, venous dilatation, and cotton wool spots, whereas CRVO was defined as intraretinal haemorrhages in all four quadrants with dilated and tortuous veins and variable optic disc oedema, cotton wool spots, and arteriolar attenuation. We excluded conference abstracts, editorials, opinion pieces, perspectives, commentary letters, and studies which did not report pre-specified review outcomes. We placed no limitation on language or publication period.

Search Methods for Identifying Studies

We searched MEDLINE (Ovid), Embase (Ovid), and the Cochrane Library from inception to 2 December 2020. Our search strategy contained comprehensive terms for NLR, PLR, and RVO (Online Supplement). We screened the reference and citation lists of included publications for further potentially relevant studies which may have been missed during our initial database search.

Study Selection

Two review authors (Z.L. and L.A.P.) independently screened titles and abstracts of search results for potentially relevant studies, then independently assessed the full texts of studies identified as potentially relevant against the eligibility criteria using Covidence (Veritas Health Innovation 2020). A third author (D.R.) adjudicated any disagreements.

Data Collection

Two review authors (Z.L. and L.A.P.) independently extracted data from included studies into standardised spreadsheets. We aimed to extract all relevant data including the following, although not all were reported by included studies: study design; sample size; baseline population characteristics such as average age, gender mix, and smoking status; baseline ophthalmological characteristics such as best corrected visual acuity, intraocular pressure, axial length, and retinal vascular abnormalities;

baseline haematological parameters such as full blood count and lipid studies biomarkers, as well as quantification technique; the method of RVO diagnosis; the presence of systemic comorbidities such as hypertension, diabetes mellitus, and chronic kidney disease; type of RVO (BRVO/CRVO/not specified); RVO disease and treatment complications such as macular oedema, retinal and anterior segment neovascularisation and its complications including vitreous haemorrhage and neovascular glaucoma, macular capillary nonperfusion, vision loss, and treatment resistance (for example, to anti–vascular endothelial growth factor therapy); and NLR and PLR measurements. Where studies compared NLR and PLR levels between groups with and without RVO, we standardised reported data into mean and standard deviation and calculated mean differences to measure effect size (Wan et al. 2014).

Assessment of Methodological Quality

Two review authors (Z.L. and L.A.P.) independently assessed study risk of bias using the Newcastle-Ottawa Quality Assessment Scale (NOS) (Wells et al. 2009). A third author (D.R.) adjudicated any discrepancies. The NOS for case-control studies comprises a 'star system' where 8 items are allocated along 3 subscales – selection, comparability, and exposure – and ranges from 0 stars (worst) to 9 stars (best). We considered a study with a star count of 7 or higher as being of high quality, 5 or higher as fair quality, and 4 or lower as poor quality. This grading was in line with previously published literature (Islam et al. 2016; Buckthorpe et al. 2019; Ji et al. 2019), given that explicit and universally accepted guidance for what constitutes a high-quality study as assessed by the NOS was not available at the time of writing.

Data Synthesis and Analysis

We tabulated mean differences (MDs) and 95% confidence intervals (CIs) in NLR and PLR measurements between RVO and control groups for each included study and used random effects inverse variance modelling to combine individual study estimates into pooled estimates. Where possible, we also performed additional analyses for BRVO and CRVO separately.

We estimated statistical heterogeneity using the I^2 statistic for each outcome, in accordance with recommendations from the Cochrane Handbook for Systematic Reviews of Interventions (Deeks JJ et al. 2020). Where reporting of prespecified covariates was sufficient, we used meta-regressions to explore possible sources of heterogeneity through inputting these covariates into the random effects model. Meta-regression creates a regression coefficient and p-value that describes how each prespecified covariate modifies the association between NLR/PLR and RVO (in other words, how each covariate modifies the MD), and the statistical significance of any observed effects. Each covariate's percentage contribution to total statistical heterogeneity (I^2 statistic) and residual

heterogeneity after the covariate is accounted for is also quantified in the meta-regression output. In this way, meta-regression explores sources of statistical heterogeneity by both quantifying the extent of heterogeneity accounted for by the covariate and whether it significantly influences the MD. If this influence is statistically significant, whether this influence is of a clinically significant magnitude can then be determined. We prespecified the following covariates for our systematic review and meta-analysis for both RVO and control groups: study characteristics (prospective vs retrospective design, methodological quality out of 9 stars as per the NOS, number of covariates reported/accounted for, publication year, number of participants, and male prevalence); patient attributes (mean age and standard deviation, and BMI); clinical ophthalmological features (best corrected visual acuity and intraocular pressure); other haematological biomarkers (total blood cholesterol, white cell count, haematocrit, haemoglobin, and triglycerides); and patient comorbidities (prevalence of smoking, hypertension, cardiovascular disease, diabetes mellitus, and chronic kidney disease).

Where studies used logistic regression to determine whether NLR and PLR were independent predictors of RVO, we performed a descriptive analysis, noting both magnitude and significance of the odd ratios reported. Where studies used receiver operating characteristic (ROC) analysis to identify the trade-off between sensitivity and specificity for NLR and PLR in differing between those with and without RVO, we noted optimised cut-off values, areas under the ROC curve (AUCs), sensitivities, specificities, and associated 95% CIs. From these, we calculated true positive, false positive, false negative, and true negative rates, and, where appropriate, generated Bayesian Summary ROC (BSROC) curves and summary sensitivity, specificity, and AUC statistics using a bivariate Bayesian modelling approach (Verde 2010).

Sensitivity analyses were conducted to assess the change in estimates following the removal of studies deemed to not be of high quality. We used visual assessment of funnel plot asymmetry and Egger's regression asymmetry test to estimate publication bias (Sterne & Egger 2001). We used the R (R Core Team 2020) statistical packages 'metafor' (Viechtbauer 2010) and 'bamdit' (Verde 2018) to perform all statistical analyses and generate figures.

Results

Search Results

Our search returned 39 results. Nine duplicates were removed, after which we screened the titles and abstracts of 30 studies. A total of 17 publications were removed following initial screening. We reviewed the full-texts of the remaining 13 studies, and excluded 5 more publications that did not meet eligibility criteria. We included 8 studies in the final review (Figure 1).

Description of Included Studies

The 8 included studies encompassed 1,059 patients, and were published between 2015 and 2020 (Dursun et al. 2015; Turkseven Kumral et al. 2016; Atum et al. 2019; Zhang et al. 2019; Zhu & Liu 2019; Kurtul et al. 2020; Pinna et al. 2020; Sahin et al. 2020). All were case-control studies. All studies used fundus examination criteria for RVO diagnosis; in addition, 3 studies reported use of fluorescein angiography for RVO diagnosis (Atum et al. 2019; Kurtul et al. 2020; Pinna et al. 2020). Characteristics of included studies are described in Table 1.

Methodological Quality

Seven studies were deemed high quality on the NOS. One study was identified as fair quality (Turkseven Kumral et al. 2016) due to unclear reporting of selection criteria. No study was judged to be of poor quality (Table 2).

Analyses

NLR

RVO

We combined 8 studies involving 1,059 patients investigating NLR measurement differences between RVO and control patients. Pooled data found that individuals with RVO had significantly elevated NLR (pooled MD 0.63, 95% CI 0.31–0.95, p=0.0001) compared to those without RVO (Figure 2a). Statistical heterogeneity was considerable (I^2=90.0%).

Three studies (Atum et al. 2019; Zhang et al. 2019; Sahin et al. 2020) performed logistic regression analysis evaluating elevated NLR as an independent predictor of RVO. Atum et al. (Atum et al. 2019), Şahin et al. (Sahin et al. 2020), and Zhang et al. (Zhang et al. 2019) reported odds ratios of 1.71 (95% CI 1.15–2.55, p=0.009), 3.89 (95% CI 1.83–8.25, p=0.001), and 1.75 (95% CI 1.15–2.65, p=0.008) respectively.

Five studies (Dursun et al. 2015; Atum et al. 2019; Zhang et al. 2019; Zhu & Liu 2019; Sahin et al. 2020) performed ROC analysis to quantify the ability of NLR to differ between people with and without RVO both sensitively and specifically (Table 3). We generated BSROC curves to graphically depict differential accuracy for NLR and RVO (Figure 3). The pooled sensitivity was 0.629 (95% credible interval (CrI) 0.284–0.872), specificity was 0.731 (95% CrI 0.373–0.934) and AUC was 0.688 (95% CrI 0.358–0.872).

One study (Turkseven Kumral et al. 2016) identified as being of fair methodological quality was removed in sensitivity analysis. Resulting NLR differences were slightly higher and statistically significant (MD 0.68 [95% CI 0.31–1.04], p=0.0003) yet statistically heterogeneity remained considerable (I^2=91.6%).

Egger's regression test for funnel plot asymmetry and visual assessment of skew for funnel plot asymmetry did not detect significant publication bias (p=0.1269) (Figure 4).

BRVO

We combined 4 studies involving 619 patients investigating NLR measurement differences between BRVO and non BRVO patients and found that individuals with BRVO had significantly elevated NLR compared with controls (pooled MD 0.76, 95% CI 0.38–1.14, p<0.0001). (Figure 2b). Statistical heterogeneity was substantial (I^2=82.3%).

Atum et al. (Atum et al. 2019) performed logistic regression analysis evaluating elevated NLR as an independent predictor of BRVO, reporting an odds ratio of 1.71 (95% CI 1.15–2.55, p=0.009). Two studies (Atum et al. 2019; Zhu & Liu 2019) performed ROC analysis to quantify NLR's ability to differ between people with and without BRVO both sensitively and specifically (Table 3).

A sensitivity analysis was performed by removing one study (Turkseven Kumral et al. 2016) identified as being of fair methodological quality. The resulting MD was slightly higher and statistically significant (MD 0.89 [95% CI 0.49–1.28], p<0.0001). Statistical heterogeneity remained substantial (I^2=79.8%).

CRVO

One study involving 254 patients investigated NLR measurement differences between CRVO and non CRVO patients, and found the CRVO group had a higher NLR, but the result was not statistically significant (MD 0.14 [95% CI -0.11–0.39], p=0.26) (Figure 2c).

PLR

RVO

We combined 6 studies involving 922 patients investigating PLR measurement differences between RVO and control patients. Pooled analysis showed that compared to controls, individuals with RVO had significantly elevated PLR (pooled MD 21.49, 95% CI 10.03–32.95, p=0.0002) (Figure 5a). Statistical heterogeneity was substantial (I^2=74.6%).

Two studies (Atum et al. 2019; Sahin et al. 2020) performed logistic regression analysis evaluating elevated PLR as an independent predictor of RVO. Atum et al. (Atum et al. 2019) and Şahin et al. (Sahin et al. 2020) reported odds ratios of 1.00 (95% CI 1.00–1.01, p=0.116) and 1.02 (95% CI 1.01–1.03, p=0.002) respectively.

Four studies (Atum et al. 2019; Zhu & Liu 2019; Kurtul et al. 2020; Sahin et al. 2020) performed ROC analysis to quantify the ability of PLR to differ between people with and without RVO both sensitively and specifically (Table 3). The pooled sensitivity was 0.645 (95% CrI 0.456–0.779), specificity was 0.616 (95% CrI 0.428–0.761) and AUC was 0.621 (95% CrI 0.452–0.741).

BRVO

We combined 3 studies involving 562 patients investigating PLR measurement differences between RVO and control patients, found the BRVO group had a higher PLR, but the result was not statistically significant (MD 19.09 [95% CI -2.97–41.15], p=0.0899) (Figure 5b). Statistical heterogeneity was considerable (I^2=86.7%).

Atum et al. (Atum et al. 2019) performed logistic regression analysis evaluating elevated PLR as an independent predictor of BRVO, reporting an odds ratio of 1.00 (95% CI 1.00–1.01, p=0.116). Two studies (Atum et al. 2019; Zhu & Liu 2019) performed ROC analysis to quantify the ability of PLR to differ between people with and without BRVO both sensitively and specifically (Table 3).

CRVO

One study involving 254 patients investigated PLR measurement differences between CRVO and non CRVO patients, and found the CRVO group had a higher PLR, but the result was not statistically significant (MD 7.33 [95% CI -10.56–25.22], p=0.27) (Figure 5c).

Meta-regression

Meta-regression of pre-specified covariates were used to investigate a considerable degree of statistical heterogeneity (I^2 statistic 90.0%) in the analysis of NLR in RVO, to identify whether they were statistically significant modifiers of the MD. Of the 21 prespecified covariates above, only 10 could be accounted for in the meta-regression due to inconsistent reporting between studies. The mean and standard deviation of age and diabetes mellitus prevalence were identified as contributors to statistical heterogeneity; of these, none were statistically significant modifiers of the MD (Table 4).

We could not perform meta-regression for the other analyses due to an insufficient number of studies for analysis.

Discussion

To our knowledge, this is the first systematic review and meta-analysis investigating the association of NLR and PLR with RVO. We show that both NLR and PLR are significantly elevated in RVO patients compared to controls. In individuals with BRVO, we demonstrate a significant elevation of NLR compared to controls. Methodological quality assessed by the NOS was generally sound, with all but one study being of high quality and low risk of bias. Sensitivity analyses removing this study demonstrated consistency of results, and methodological quality out of nine stars was not a significant effect size modifier where meta-regression was possible. Studies were substantially or considerably heterogeneous. Meta-regression revealed mean and standard deviation of age and diabetes mellitus prevalence to be contributors to statistical heterogeneity in the analysis of pooled NLR in RVO. However, none were statistically significant effect modifiers.

Interestingly, despite PLR being significantly elevated in general RVO patients, this effect was not significant in both constituent BRVO and CRVO. We posit that this is possibly explained by our subgroup analyses not being powered to detect small differences in the setting of reduced sample size with the RVO group being split into its component groups. Moreover, multiple studies which reported PLR in RVO patients did further clarify the specific subtype of RVO as BRVO, CRVO, or both. As such, these studies could not be included in subgroup analysis, leading to further diminished sample size and reduction in statistical power.

Leucocytes exert well described roles in immune response modulation in both atherosclerosis and cardiovascular disease, (Horne et al. 2005) with both neutrophilia (Uthamalingam et al. 2011) and lymphopenia (Bian et al. 2010) conferring a poorer prognosis. As the ratio of neutrophils to lymphocytes, NLR has also been found to be elevated in atherosclerosis (Balta et al. 2016) and cardiovascular disease (Afari & Bhat 2016). More importantly, elevations in NLR have, in recent years, been also found to be of predictive value (both diagnostic and prognostic) in a range of cardiovascular (Kalay et al. 2012; Borg Caruana et al. 2020; Jackson et al. 2020; Liu et al. 2020) and ophthalmic conditions such as diabetic retinopathy and age-related macular degeneration (Ulu et al. 2013; Ilhan et al. 2015). The PLR is a similar emerging inflammatory biomarker that elevates in thrombocytosis and lymphopenia. Both platelet activation and systemic inflammation – with upregulation of prothrombotic cytokines such as interleukin-1β, interleukin-6, tumour necrosis factor-α, and homocysteine in the latter – may predispose to RVO (Chua et al. 2005; Liu et al. 2021) and other ophthalmic diseases such as glaucoma (Ozgonul et al. 2016) and age-related macular

degeneration (Sengul et al. 2017). Additionally, aqueous markers of platelet activation are elevated in RVO (Cehofski et al. 2020). The relationship between NLR and PLR with many RVO risk factors explored in this paragraph is well established; our study supports an association between NLR and PLR with RVO itself.

Our results should be considered in light of the following limitations. First, while we were able to perform sensitivity analyses removing all but high-quality methodological studies in the meta-analysis, and we were able to perform meta-regression for the NLR analysis to identify several contributors to heterogeneity, residual heterogeneity was considerable. Second, low study numbers meant that meta-regression could not be performed in some subgroups, or may not have been sufficiently powered to detect all associations. Additionally, publication bias could not be estimated for all analyses due to insufficient study number. Moreover, the observational nature of included studies meant that only correlation, rather than causation, could be inferred. Lastly, lack of comprehensive population characteristics reporting in some studies, and lack of reporting of certain characteristics across all studies meant that not all prespecified covariates–risk factors, comorbidities, or complications of RVO itself–could undergo meta-regression. Further studies with comprehensive baseline reporting could allow more extensive characterisation of heterogeneity and lend robustness to our results.

Many opportunities for future research emerged from our study. Whether or not an elevated NLR or PLR could be prognostic for clinically significant outcome measures such as macular oedema, retinal and anterior segment neovascularisation, macular capillary nonperfusion, and vision loss, or whether they could be used to assist in risk stratification or severity assessment like in diabetic retinopathy (Ulu et al. 2013) remains under investigated. Given that all included studies were retrospective in nature, high-quality prospective studies would be valuable. Based off these studies, ROC-optimised threshold values for NLR and PLR could be established for important clinical outcomes such as those aforementioned. Additionally, at time of writing, Pinna et al.'s findings (Pinna et al. 2020) represented the only study that investigated the association of NLR and PLR with CRVO. Although rarer in prevalence, the visual complications of CRVO are severe, and further validation of these results is important. Moreover, while meta-regression did not detect significant effect modifiers, this does not rule out potential associations. The inclusion of further high-quality original research studies into the analysis would increase meta-regression power to provide further clarity, for covariates like age and diabetes prevalence in particular. Furthermore, given the well-documented associations of NLR and PLR with systemic cardiovascular disease (Angkananard et al. 2018; Kurtul & Ornek 2019) and the association of RVO with cardiovascular disease and its risk factors as described previously, whether or not NLR and PLR could aid in individualising RVO aetiological workup or cardiovascular risk stratification in patients with RVO could be investigated. Lastly, while this review focused on NLR and PLR, other haematological biomarkers such as mean platelet volume and platelet

distribution width have also been found be associated with RVO (Liu et al. 2021). The integration of a range of haematological and non-haematological biomarkers into predictive models could enhance all aspects of disease assessment, management, and complication prevention.

Conclusion

This systematic review and meta-analysis found that NLR and PLR are significantly elevated in patients with RVO compared to controls. Further research is needed to investigate the potential prognostic value and independence of these findings.

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The authors declare that there is no conflict of interest.

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Figure Legends

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart. Reasons for full text exclusions: 1 lack of NLR or PLR reporting, 1 no control group, and 3 inappropriate formats (conference abstract or letter). Of the 8 included studies, 3 reported NLR or PLR measurements for BRVO only, 1 reported measurements for both BRVO and CRVO, and 4 reported measurements for RVO generally without specifying subtype.

Figure 2: a) Forest plot showing elevated NLR in RVO+ vs RVO- patients. b) Forest plot showing elevated NLR in BRVO+ vs BRVO- patients. c) Forest plot showing no significant difference in NLR in CRVO+ vs CRVO- patients. NLR=Neutrophil-Lymphocyte Ratio, RVO=Retinal Vein Occlusion, BRVO=Branch Retinal Vein Occlusion, CRVO=Central Retinal Vein Occlusion.

Figure 3: Bayesian summary receiver operating characteristic curve showing summary differential ability of NLR in those with and without RVO, with upper and lower 95% credible bands. Each filled circle represents one included study, the size of which is weighted in proportion to the study's sample size.

Figure 4: Funnel plot for visual assessment of publication bias in the NLR in RVO analysis.

Figure 5: a) Forest plot showing elevated PLR in RVO+ vs RVO- patients. b) Forest plot showing no significant difference in PLR in BRVO+ vs BRVO- patients. c) Forest plot showing no significant difference in PLR in CRVO+ vs CRVO- patients. PLR=Platelet-Lymphocyte Ratio, RVO=Retinal Vein Occlusion, BRVO=Branch Retinal Vein Occlusion, CRVO=Central Retinal Vein Occlusion.

Table 1: Characteristics of Included Studies.

Study ID	Study design	Patients (n)	Age±SD (years)	Male prevalence (%)	Hypertension prevalence (%)	Diabetes mellitus prevalence (%)	Smoking prevalence (%)	Ratio measured (NLR and/or PLR)	Biomarker quantification	RVO subtype specified (BRVO and/or CRVO)
Atum 2019	Retrospective	146	58.2±11.4	44.5	30.1	0.0	Not reported	NLR PLR	Cell-Dyn 3700 Hematology Analyzer (Abbott Diagnostics, Santa Clara, CA, USA)	BRVO
Dursun 2015	Retrospective	80	63.0±11.0	49.6	40.0	0.0	0.0	NLR	Beckman Coulter Automated CBC Analyzer (Beckman Coulter, Fullerton, CA, USA)	Not specified
Kurtul 2020	Retrospective	64	61.5±11.1	57.8	35.9	0.0	0.0	NLR PLR	Mindray BC Hematology Analyzer (Mindray, Huntingdon, UK)	Not specified

Pinna 2020	Retrospective	254	70.7±11.5	61.4	50.8	11.8	Not reported	NLR PLR	Cell-Dyn Sapphire Hematology Analyzer (Abbott Diagnostics, Santa Clara, CA, USA)	BRVO CRVO
Şahin 2019	Retrospective	199	57.1±15.5	45.7	26.6	6.5	0.0	NLR PLR	Cell-Dyn 3700 Hematology Analyzer (Abbott Diagnostics, Santa Clara, CA, USA)	Not specified
Türkseven Kumral 2016	Not reported	57	63.0±10.5	43.9	100.0	0.0	0.0	NLR	Cell-Dyn 3700 Hematology Analyzer (Abbott Diagnostics, Santa Clara, CA, USA)	BRVO
Zhang 2019	Retrospective	97	55.6±11.5	67.0	48.5	17.5	Not reported	NLR PLR	Mindray BC-5500 Hematology Analyzer (Mindray, Shenzhen, China)	Not specified

Zhu 2019	Retrospective	162	60.6±1.4	60.5	70.4	0.0	0.0	NLR PLR	Sysmex KX-21 Hematology Analyzer (Sysmex, Kobe, Japan)	BRVO

NLR = Neutrophil-Lymphocyte Ratio, PLT = Platelet-Lymphocyte Ratio, RVO = Retinal Vein Occlusion, BRVO = Branch Retinal Vein Occlusion, CRVO = Central Retinal Vein Occlusion.

Table 2: Assessment of Methodological Quality (Newcastle-Ottawa Scale)

Newcastle-Ottawa Scale	OVERALL ASSESSMENT	Selection					Comparability	Exposure		
		Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	subtotal	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate
Study		a) yes, with independent validation* b) yes, eg record linkage or based on self reports c) no description	a) consecutive or obviously representative series of cases* b) potential for selection biases or not stated	a) community controls* b) hospital controls c) no description	a) no history of disease (endpoint)* b) no description of source		a) Study controls for age* b) Study controls for hypertension*	a) secure record (eg surgical records)* b) structured interview where blind to case/control status* c) interview not blinded to case/control status d) written self report or	a) Yes* b) No	a) same rate for both groups* b) non respondents described c) rate different and no designation

								medical record only e) no description		
Atum 2019	8	1	0	1	1	3	2	1	1	1
Dursun 2015	8	1	0	1	1	3	2	1	1	1
Kurtul 2020	8	1	0	1	1	3	2	1	1	1
Pinna 2020	9	1	1	1	1	4	2	1	1	1
Sahin 2019	9	1	1	1	1	4	2	1	1	1
Turkseven Kumral 2016	5	0	0	0	1	1	1	1	1	1
Zhang 2019	8	1	0	1	1	3	2	1	1	1
Zhu 2019	7	0	0	1	1	2	2	1	1	1

We considered a study with a star count of 7 or higher as being of high quality, 5 or higher as fair quality, and 4 or lower as poor quality.

Table 3: ROC Analysis of NLR and PLR in RVO

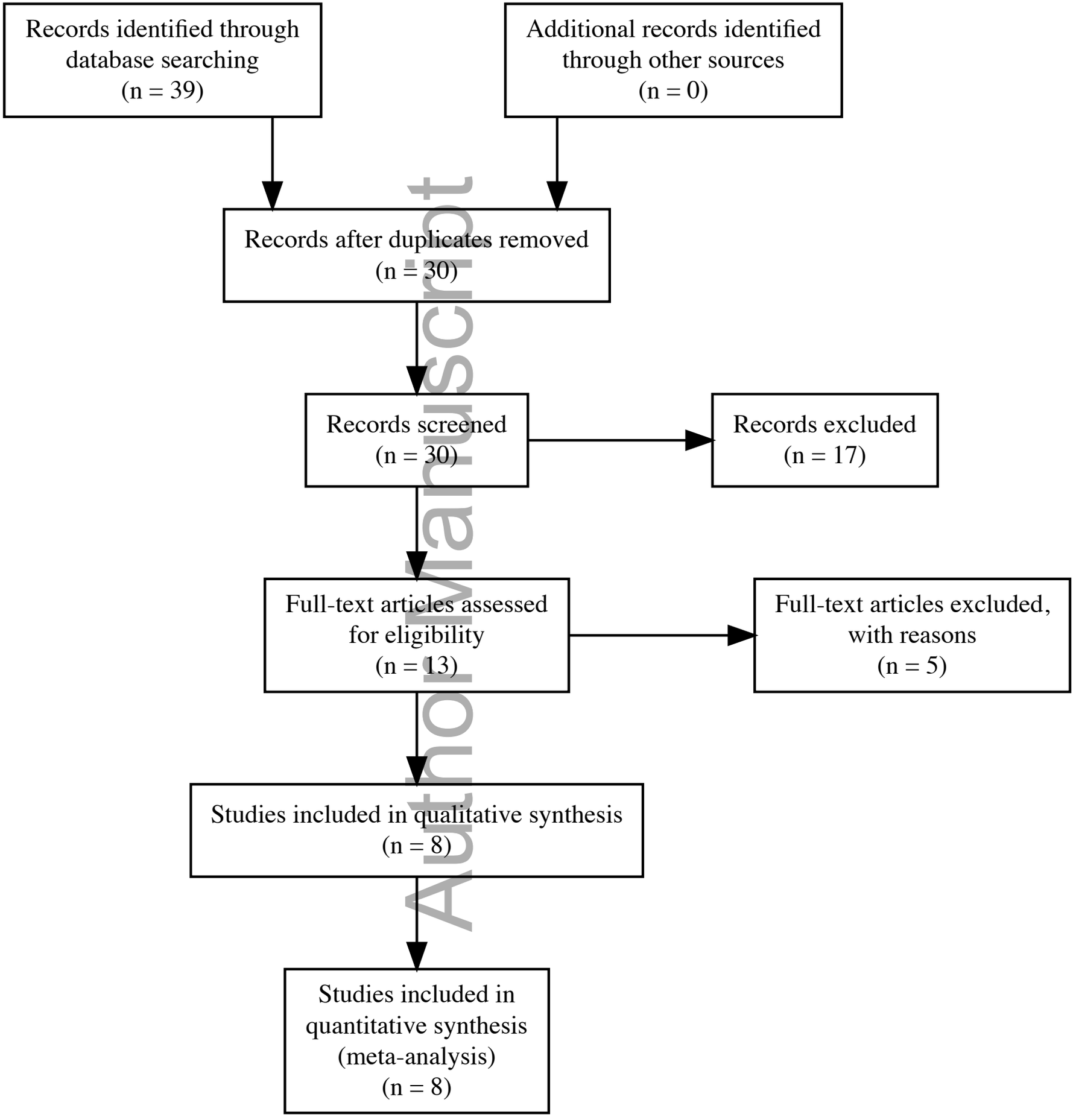
		Study ID	Optimal ROC Cut-Off	AUC	95% CI	Sensitivity	Specificity
NLR	RVO	Atum 2019	1.78	0.65	(0.56, 0.73)	0.60	0.58
		Dursun 2015	1.89	0.88	(0.79, 0.94)	0.73	1.00
		Şahin 2020	1.63	Not Reported	Not Reported	0.65	0.68
		Zhang 2019	1.83	0.68	(0.57, 0.79)	0.84	0.58
		Zhu 2019	2.48	0.82	(0.75, 0.88)	0.58	0.98
	BRVO	Atum 2019	1.78	0.65	(0.56, 0.73)	0.60	0.58
		Zhu 2019	2.48	0.82	(0.75, 0.88)	0.58	0.98
	CRVO	-	-	-	-	-	-
PLR	RVO	Atum 2019	109.95	0.56	(0.47, 0.66)	0.55	0.55
		Kurtul 2020	123.00	0.73	(0.60, 0.85)	0.69	0.72
		Şahin 2020	98.50	Not Reported	Not Reported	0.70	0.58
		Zhu 2019	110.20	0.78	(0.70, 0.84)	0.72	0.72
	BRVO	Atum 2019	109.95	0.56	(0.47, 0.66)	0.55	0.55
		Zhu 2019	110.20	0.78	(0.70, 0.84)	0.72	0.72
	CRVO	-	-	-	-	-	-

ROC = Receiver Operating Characteristic, NLR = Neutrophil-Lymphocyte Ratio, PLT = Platelet-Lymphocyte Ratio, RVO = Retinal Vein Occlusion, BRVO = Branch Retinal Vein Occlusion, CRVO = Central Retinal Vein Occlusion, AUC = Area Under the ROC Curve.

Table 4: Meta-regression of NLR in RVO

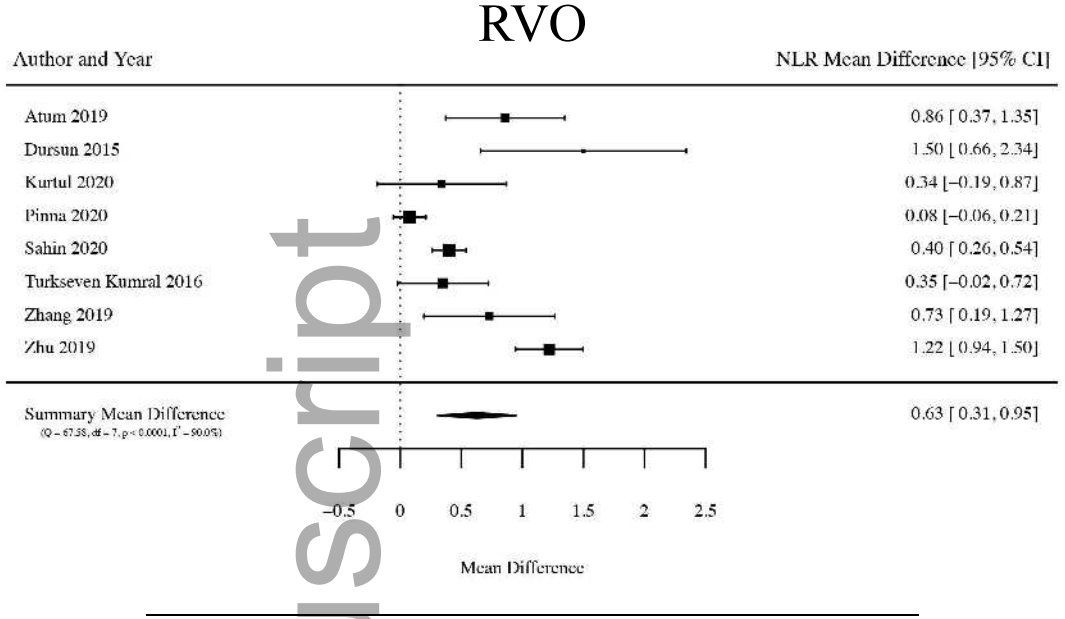
Covariate	k	Regression coefficient – magnitude of effect size modification	p-value	95% CI (lb, ub)	Heterogeneity accounted for	Residual Heterogeneity (I^2)
Standard Deviation of Age	8	-0.0613	0.0673	-0.1270 0.0044	36.00%	83.36%
Mean Age	8	-0.0379	0.2952	-0.1040 0.0281	8.43%	82.25%
Diabetes mellitus prevalence	8	-2.6680	0.2176	-7.6638 2.3278	6.26%	88.05%
Male Prevalence	8	0.5915	0.7799	-3.5576 4.7407	0.00%	87.81%
Hypertension prevalence	7	1.0284	0.4352	-1.5547 3.6115	0.00%	89.21%
Sample size	8	-0.0019	0.2761	-0.0068 0.0030	0.00%	89.72%
Publication Year	8	-0.1127	0.2571	-0.3076 0.0822	0.00%	90.38%
NOS Score	8	-0.0580	0.6756	-0.3299	0.00%	93.16%

				0.2138		
Smoking prevalence	5	N/A as all reporting studies had smoking as part of exclusion criteria				
Study Design	7	N/A as all reporting studies were retrospective				



NLR

a)



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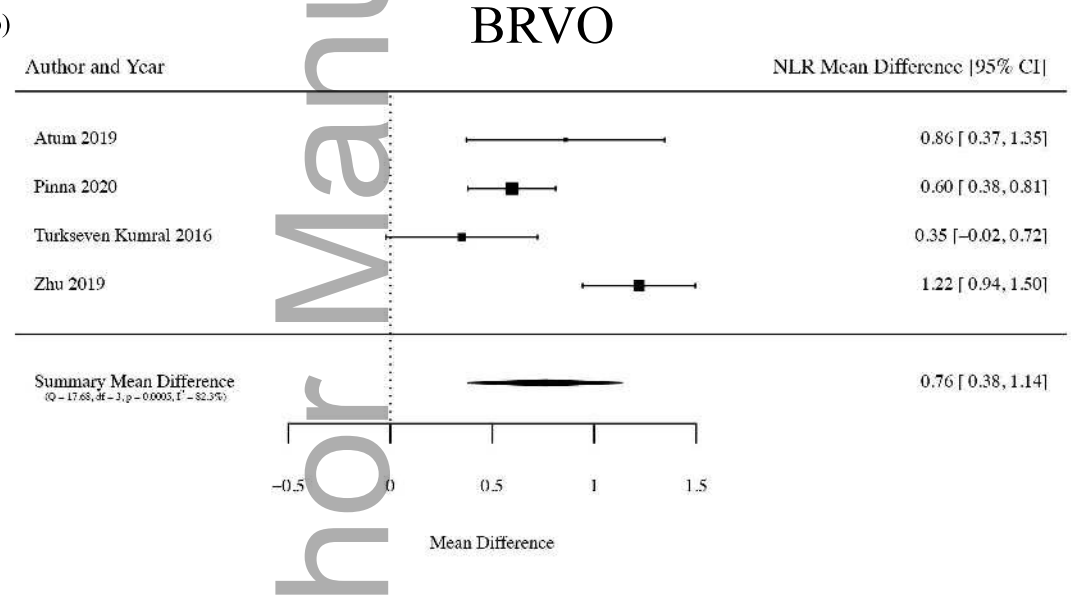

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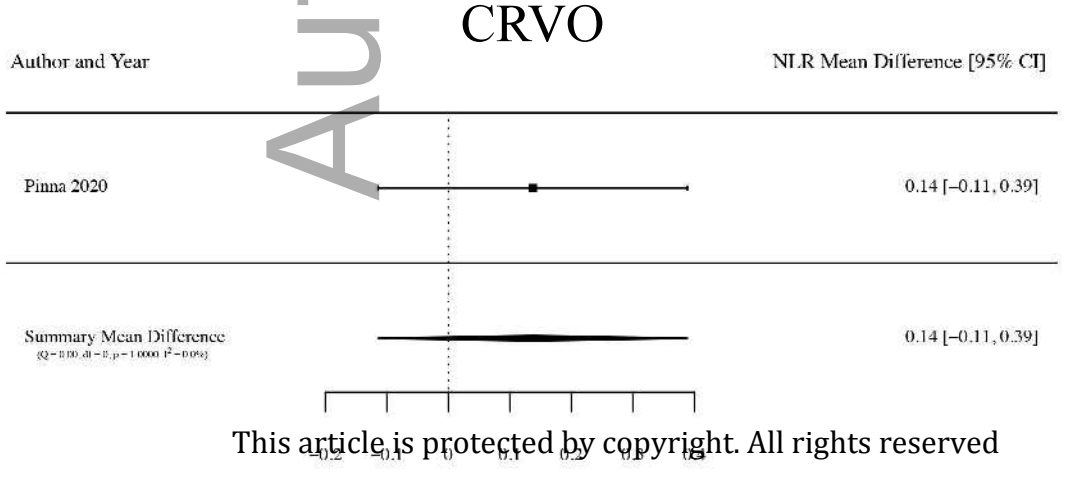
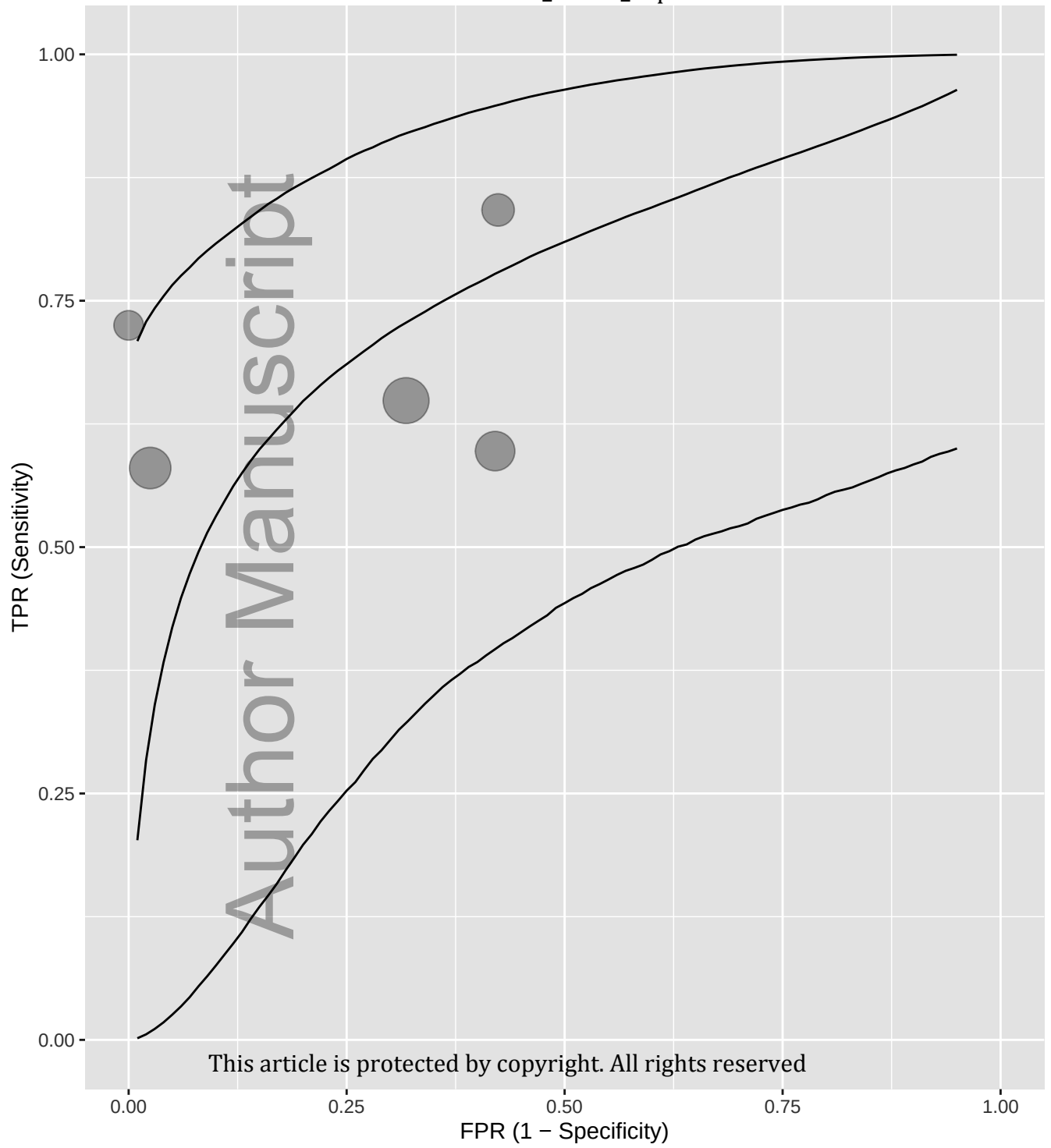
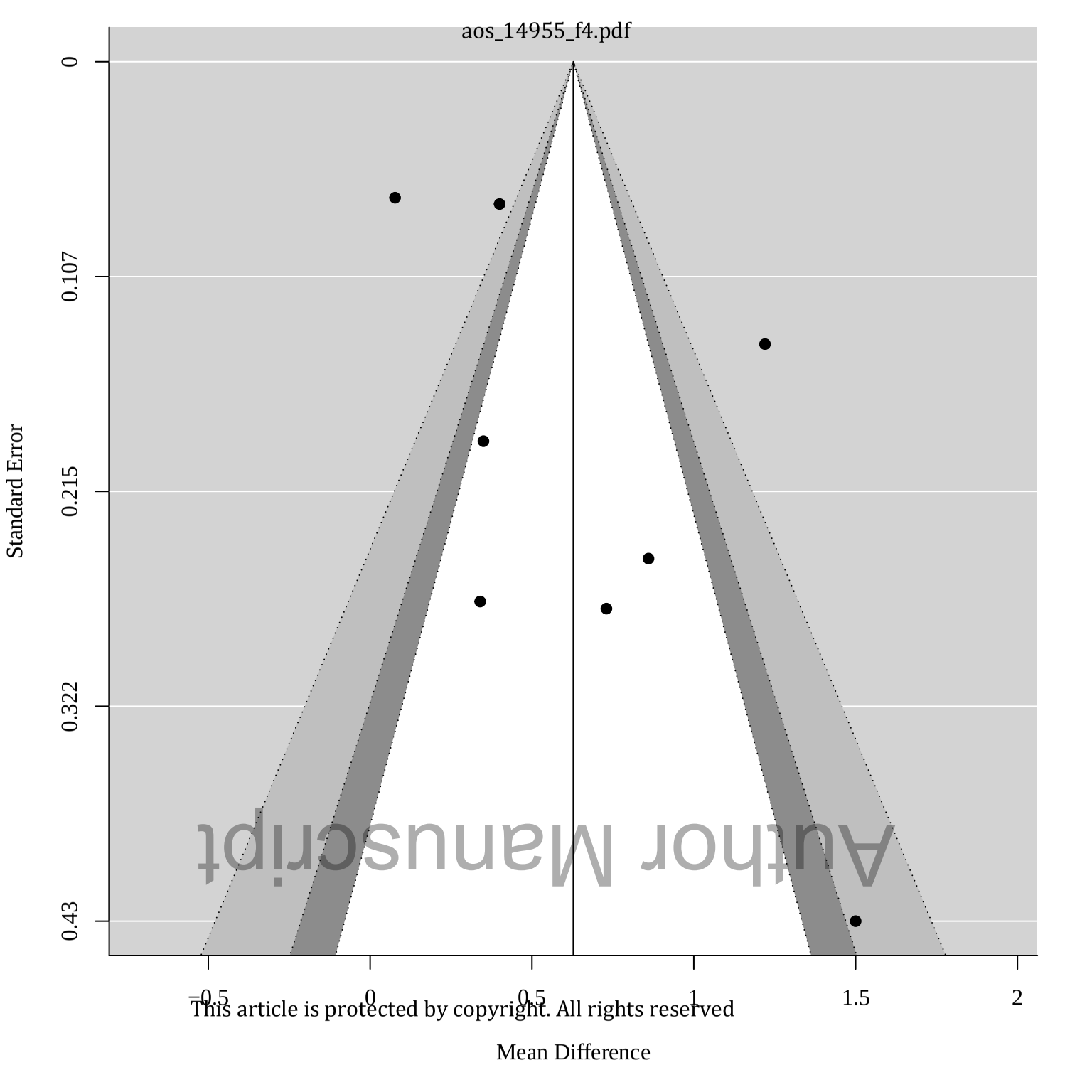


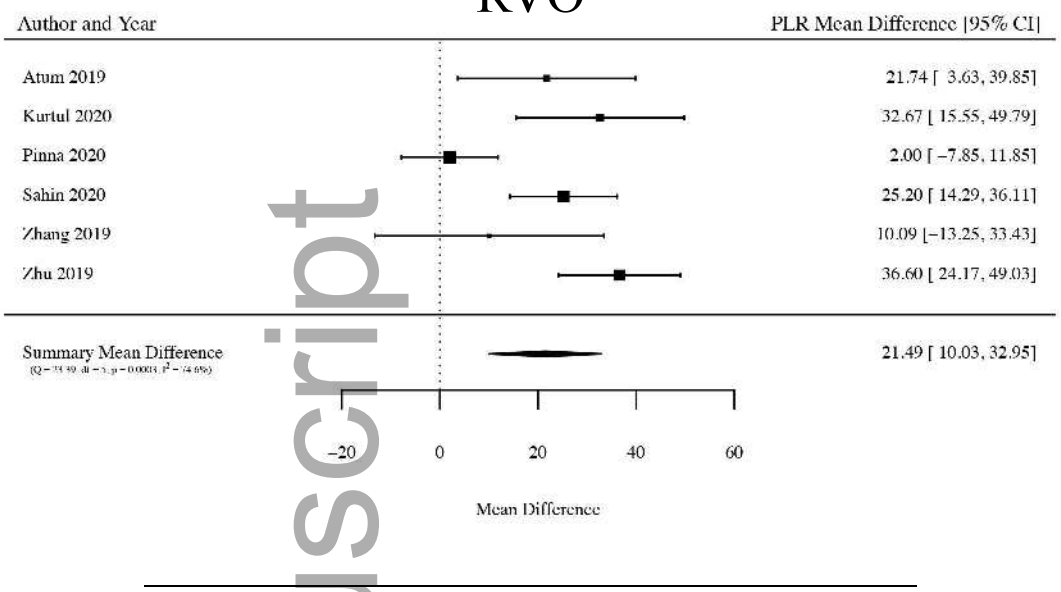




PLR

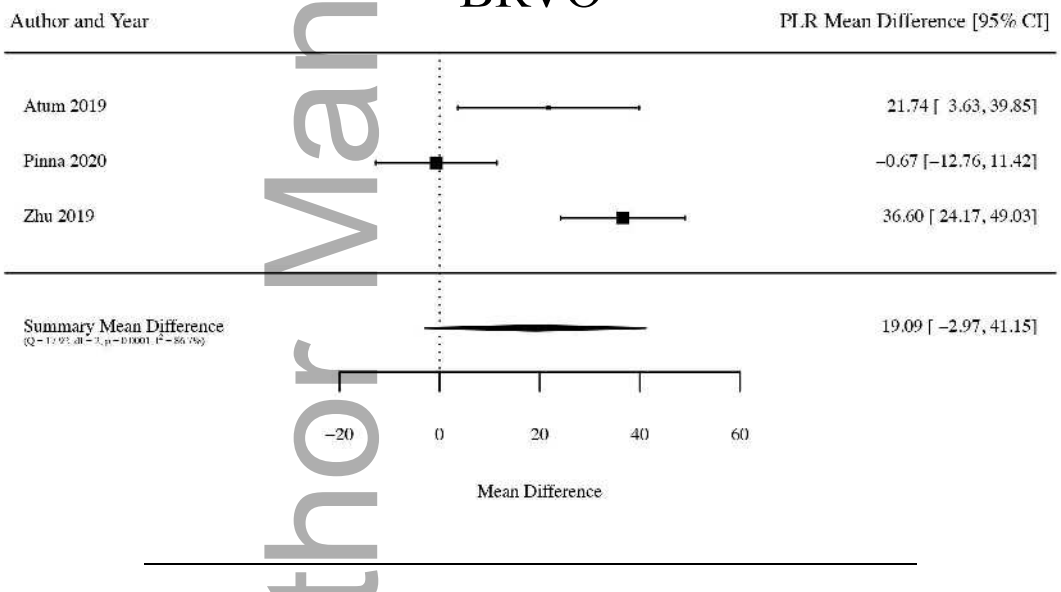
a)

RVO



b)

BRVO



c)

CRVO