Systematic Review

Evaluating the Efficacy of Anti-VEGF versus Laser Therapy in Zone 1 & Zone 2 Retinopathy of Prematurity: A Systematic Review & Meta-Analysis

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Fatrin Patrycia Salim[1], Rivaldo Steven Heriyanto[2], Regan Elbert[3]
[1-3]Department of Ophthalmology, Faculty of Medicine Universitas Pelita Harapan, Siloam Hospital Lippo Village, Tangerang, Banten, Indonesia

ABSTRACT

Database searches were conducted across PubMed, Science Direct, CENTRAL, and Scopus, up to December 6th, 2024, to evaluate efficacy of Anti-VEGF Versus Laser Therapy in Zone 1 & Zone 2 Retinopathy of Prematurity. Anti-VEGF treatment showed significant superiority in initial regression for zone 1 ROP (OR: 2.95; 95% CI: 1.55, 5.61; p = 0.001), however, in zone 2 ROP, there were no significant differences. (OR: 1.15 CI: 95%: 0.59, 2.24, p = 0.67). Zone 1 ROP treated with laser photocoagulation demonstrated increased odds of recurrence after initial treatment (OR: 2.23; 95% CI: 1.25, 4.00; p=0.007), compared to lower odds of recurrence in those treated with anti-VEGF in zone 2 ROP (OR: 0.73; 95% CI: 0.56, 0.94; p=0.01). There was no significant difference in favourable outcomes (OR: 0.58; 95% CI: 0.33, 1.02; p=0.06) and (OR: 0.54; 95% CI: 0.21, 1.40; p=0.21) in both zones.

Keyword: Retinopathy of Prematurity, Anti-Vascular Endothelial Growth Factor, Laser Photocoagulation.

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Correspondence: Rivaldo Steven Heriyanto
Department of Ophthalmology, Faculty of Medicine Universitas Pelita Harapan, Siloam Hospital Lippo Village, Tangerang, Banten, Indonesia
Email: raldostvn@gmail.com

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INTRODUCTION

Retinopathy of prematurity (ROP) is a multi-factorial retinal disease that predominantly affects premature infants, characterised by abnormal growth of the blood vessels of retina.[1,2] Based on its severity, ROP is categorized into several types, with Type 1 ROP being the most severe and requiring immediate intervention.[3] "Type 1 ROP" includes any stage of the disease in Zone 1, stage 3 in Zone 2, or any ROP with plus disease, signifying profound vascular pathology. Conversely, Type 2 ROP presents with less severity, typically allowing a strategy of vigilant observation rather than urgent surgical therapy.[3]

Beyond types based on severity, anatomical location into Zones 1 and 2 is crucial for determining both prognosis and therapeutic strategies.[4] Zone 1 represents the innermost retina, and carries the highest risk for severe visual impairment, demanding prompt management.[5] Zone 2 encompasses broader retinal area. Aggressive posterior ROP is a rapidly progressive form occurring in the posterior aspect of zone 2 and is characterized by substantial vascular abnormalities and a high risk of visual impairment, prompting the need of swift and effective treatment.[6] While current treatment protocol mainly focus on the specific ROP "type", distinguishing between anatomical zones is equally vital for optimizing the choice of treatment.[7] The decision to utilize laser photocoagulation (LPC) versus anti-vascular endothelial growth factor (anti-VEGF) therapy can profoundly affect visual prognosis of the infants.[8]

This study aims to compare the efficacy of anti-VEGF agents against laser therapy, specifically in

Zone 1 and 2 cases. By reviewing both the type and zone differentiation in the treatment choice and understanding the relationship between ROP classifications, treatment strategies could be optimized, increasing outcomes for patients with ROP.

METHOD

This study adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) criteria.[9] A detailed protocol has been previously registered in PROSPERO **(CRD42024605028).** The PICOS framework of the study were as follows:

1. Population: Infants diagnosed with zone 1 and 2 ROP.
2. Intervention: Anti-vascular endothelial growth factor.
3. Control: Laser photocoagulation.
4. Outcome: Initial regression, recurrence, and unfavourable outcome.
5. Study design: Clinical trials, prospective or retrospective cohort.

The population included is defined as infants who were delivered at a gestational age of 32 weeks or less or had a birth weight of 1500 grams or below, diagnosed with ROP zone I, stage 1+, 2+, 3, or 3+, or zone II stage 2+, 3+, or AP-ROP.[1,10] The intervention includes any anti-VEGF therapy (e.g., aflibercept, bevacizumab, conbercept, ranibizumab) and any laser photocoagulation. For the outcomes, the initial regression is the number of infants without active ROP, plus disease, or a ridge that partially regressed or entirely after the first intervention protocol.[11] Recurrence is defined as recurrent plus disease, recurrent neovascularization, or progression of traction despite treatment.[12] Unfavourable outcomes included retrolental opacity, macular fold, macular dragging, or retinal detachment during the study period.

Additional exclusion criteria were applied to eliminate papers that met the following criteria: (1) studies that did not compare zone 1 and zone 2 specifically, (2) case reports, case series, letter to editors or other non-primary research, (3), research articles that were not accessible in their entirety or studies that did not undergo the process of proper publication, and (4) were not in English language.

Search Strategy and Study Selection

A thorough and systematic literature search was performed using electronic databases such as PubMed, ScienceDirect, the Cochrane Controlled Register of Trials (CENTRAL), and Scopus, encompassing all publications available as of December 6, 2024. All retrieved papers were initially evaluated for relevance by two authors, and duplicates were removed. Primary papers cited in review articles, systematic reviews, or meta-analyses that satisfied the established inclusion criteria but were overlooked during the initial screening were obtained. Subsequently, the two authors conducted a thorough evaluation of the full-text papers. Any disputes were settled through discussion involving the third author.

Two authors did data extraction. Extracted data included details such as first author, country of origin of the study, publication year, study design used, centres where the study was conducted, number of study patients, number of total eyes, treatment given and method of administration, and outcome of interest, which included initial regression, recurrence, and unfavourable outcome. Inconsistencies encountered during the data extraction were resolved through discussion.

Statistical Analysis

Meta-analysis was conducted using the "Review Manager (RevMan) Version 5.4. The Cochrane Collaboration, 2020" intervention analysis.[13] To calculate the odds ratio (OR) with a 95% confidence interval (CI) across studies, the Mantel-Haenszel technique was used. Heterogeneity is assessed by considering various participant characteristics and treatment protocols across studies. The degree of heterogeneity among the included studies was evaluated using I^2statistic; values greater than 50% indicated significant heterogeneity. Additionally, individual assessment of heterogeneity was also employed. Funnel plots were created only when more than ten studies were included, as analyses with fewer studies lack the power to detect publication bias. When heterogeneity was considered high, a random-effects analysis was used. Significance threshold was determined at $P < 0.05$, assuming a two-sided test, 80% statistical power, and 5% type I error for estimating the information size. All calculations were adjusted for heterogeneity between studies.

Two researchers conducted a systematic appraisal of bias, for randomized controlled trials, Cochrane's Risk of Bias version 2 (RoB v2) was employed, while for non-randomized studies. Risk of Bias in Non-Randomized Studies of Intervention (ROBINS-I) was used.[14]

RESULTS

Study Characteristics and Selection

Search result from four databases yielded a total of 745 studies. After duplicates removal and screening the publications based on the titles and abstracts, 716 articles were excluded from further analysis as they did not fulfil the inclusion criteria. The resulting 29 articles were selected and a comprehensive assessment was conducted on their full texts, resulting in 23 of them being excluded due to reasons such as nine articles where complete reports could not be retrieved, 8had insufficient details on outcome of interest, four articles did not have the outcome of interest, two were not in English, and seven studies were review articles. Finally, six papers satisfied the determined inclusion criteria.[10–12,15–17]A citation search was conducted from the already included studies and found 15 eligible reports based on their titles and abstracts. Of the 15 articles, 10 were not retrieved, leaving 5 to be assessed for further eligibility. Three articles were excluded, where two articles already included from primary database searching, and 1 article did not have sufficient detail on the outcome, leaving two articles to be added to the studies included in the review, totalling eight studies.[18,19] The selected publications were then subjected for further analysis, as shown in Figure 1.

Publications included were comprised of 3 RCTs and 5 comparative non-randomized studies. Characteristics of included studies are shown in Table 1. Two studies were conducted in multiple countries, two in the USA, and one each in Germany, Iran, Turkey, and China. Intravitreal Bevacizumab was the most prevalent regimen in the anti-VEGF group, being used in 6 studies, followed by Ranibizumab in 3 studies, and Conbercept and Aflibercept in one study each. As for the laser group, conventional laser photocoagulation (LPC) was the most used laser therapy applied in 6 studies, while pan-retinal photocoagulation and transscleral diode laser were used in one study each. The follow-up period across all 8 studies varied between 24 weeks to 75 weeks.

The result of the RoB v2 assessment showed that two of the three RCTs examined were classified as exhibiting a low risk of bias, while one study was classified as moderate risk of bias (Figure 2). As for the ROBINS-I assessment, four out of five observational studies were classified as having a high risk of bias.[15,16,18,19] This was primarily attributed to the lack of mention of confounding factors and the adjustment made to mitigate potential confounding (Figure 2).

Initial Regression of ROP

Meta-analysis of the included studies showed that more participants achieved initial regression when treated using anti-VEGF compared to LPC in zone 1 ROP (OR: 2.95; 95% CI: 1.55, 5.61; p = 0.001; I2: 53%). Upon "subgroup analysis "based on study design, the results were significant both in RCTs (OR: 4.74; 95% CI: 1.09, 20.57; p = 0.04; I2: 82%) and observational studies (OR: 2.26; 95% CI: 1.44, 3.55; p = 0.0004; I2: 0%). There were no significant differences observed between anti-VEGF and LPC in zone 2 ROP (OR: 1.15 95%: 0.59, 2.24, p = 0.67; I2: 72%), although when analysis based on study design was conducted separately, both RCT and observational studies yielded significant results (OR: 0.56; 95%: 0.32, 0.97, p = 0.04; I2: 16% and OR: 1.98; 95%: 1.09, 3.58, p = 0.02; I2: 29%) (Figure 3).

Recurrence

A higher recurrence was observed in patients receiving LPC in zone 1 ROP (OR: 2.23; 95% CI: 1.25, 4.00; p = 0.007; I2: 43%), compared to lower odds of recurrence in those treated with anti-VEGF in zone 2 ROP (OR: 0.73; 95% CI: 0.56, 0.94; p=0.01; I2: 85%). Additional analysis based on study design was conducted and the result was only significant among the observational studies (OR: 2.12; 95% CI: 1.43, 3.15; p=0.0002; I2: 0%) while data from RCTs showed no significant result (OR: 2.81; 95% CI: 0.63, 12.49; p = 0.17; I2: 79%). As for zone 2 ROP, when divided based on study design, a contradictory result could be observed between RCTs (OR: 2.69; 95% CI: 1.63, 4.46; p=0.0001; I2: 2%) and observational studies (OR: 0.45; 95% CI: 0.32, 0.62; p=0.00001; I2: 47%) (Figure 4).

Unfavourable Outcome

Odds for unfavourable outcomes were less in patients receiving anti-VEGF when compared to those that

Table 1: *Studies characteristics.*

No	Study ID (year)	Study duration	Study Design	Country	Multi/Single Centre	Sample Size (n)	Number of eyes (n)	Treatment		Follow-up duration
								Anti-VEGF	Laser treatment	
1	Stahl (RAINBOW) (2019)[10]	2015 -2017	RCT	26 countries	Multi (87 centres)	87	174	Ranibizumab 0·2 mg or ranibizumab 0·1 mg	Conventional LPC	24 weeks
2	Roohipoor (2018)[11]	2011-2014	Retrospective (CNS)	Iran	Single	493	986	Bevacizumab 0.625 mg/0.025 ml	Transscleral diode laser	75 weeks
3	Mintz-Hittner (BEAT-ROP) (2011)[12]	2008-2010	RCT	USA	Multi (15 centres)	150	300	Bevacizumab 0.625 mg/0.025 ml	Conventional LPC	54 weeks
4	Hwang (2015)[15]	2008-2012	Retrospective (CNS)	USA	Multi (2 centres)	28	54	Bevacizumab 0.625 mg/0.025 ml	Panretinal photocoagulation	24 weeks
5	Walz (2016)[16]	2011-2014	Retrospective (CNS)	German	Multi (9 centres)	89	177	Bevacizumab 0.625 mg/0.025 ml, Ranibizumab 0.25 mg/0.025 ml	Conventional LPC	NA
6	Stahl (FIREFLEYE) (2022)[17]	2019-2020	RCT	27 countries	Multi (64 centres)	113	218	Aflibercept 0.4-mg	Transpupillary conventional laser photocoagulation	24 weeks
7	Linghu (2022)[18]	2010-2018	Retrospective (CNS)	China	Single	862	1627	Bevacizumab 0.625 mg/0.025 ml, Ranibizumab 0.25 mg/0.025 ml, Conbercept 0.25 mg/0.025 ml	Conventional LPC	24 weeks
8	Demir (2019)[22]	2012-2017	Retrospective (CNS)	Turkey	Single	65	126	Bevacizumab 0.625 mg/0.025 ml	Conventional 810nm diode LPC	44 weeks

Abbreviation:
RCT: Randomized controlled trials
CNS: Comparative non-randomized studies
LPC: Laser photocoagulation

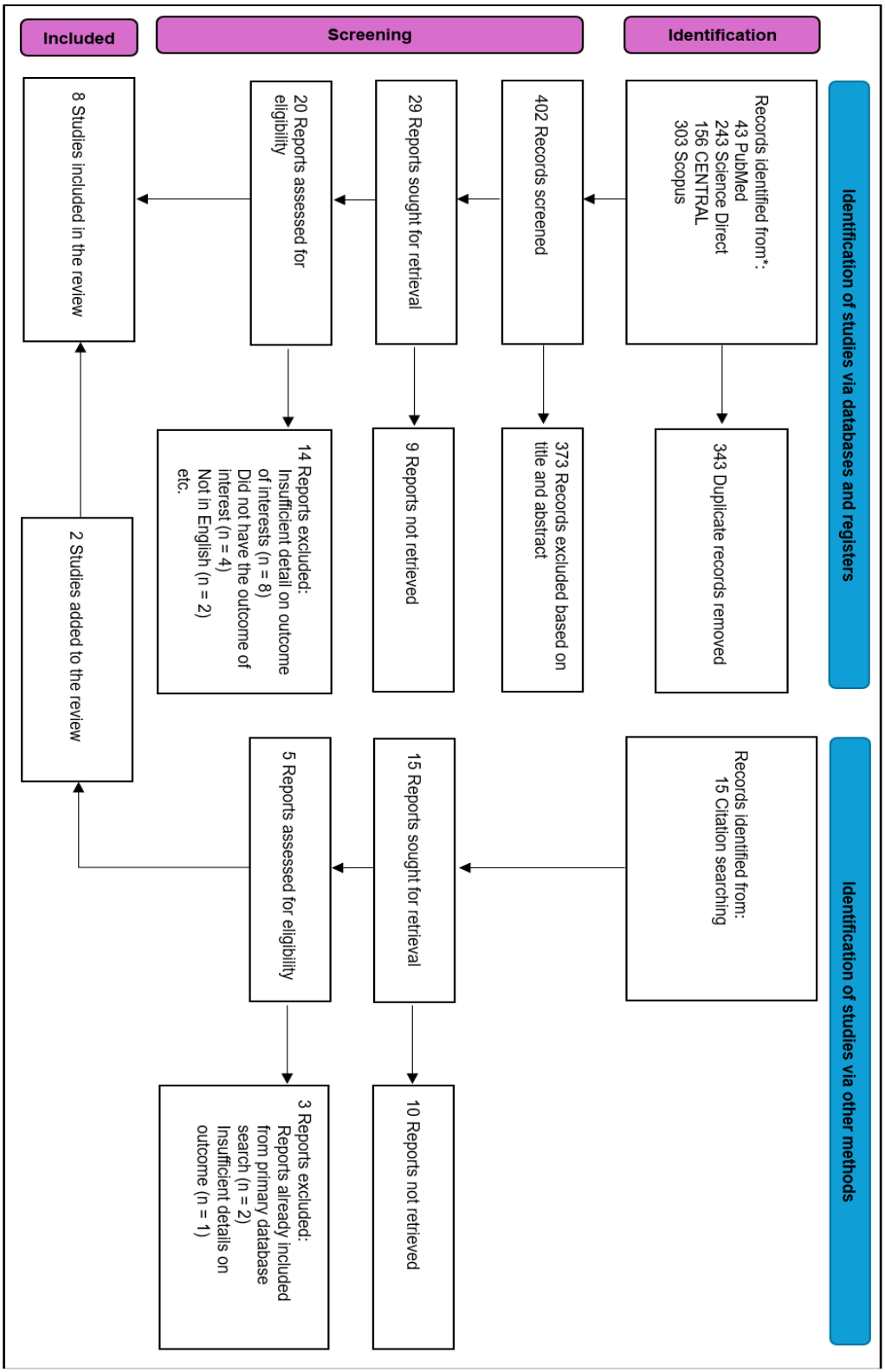

Figure 1: PRISMA diagram depicting the detailed process of study selection for the systematic review and meta-analysis.

Abbreviation:
RCT: Randomized controlled trials
CNS: Comparative non-randomized studies
LPC: Laser photocoagulation

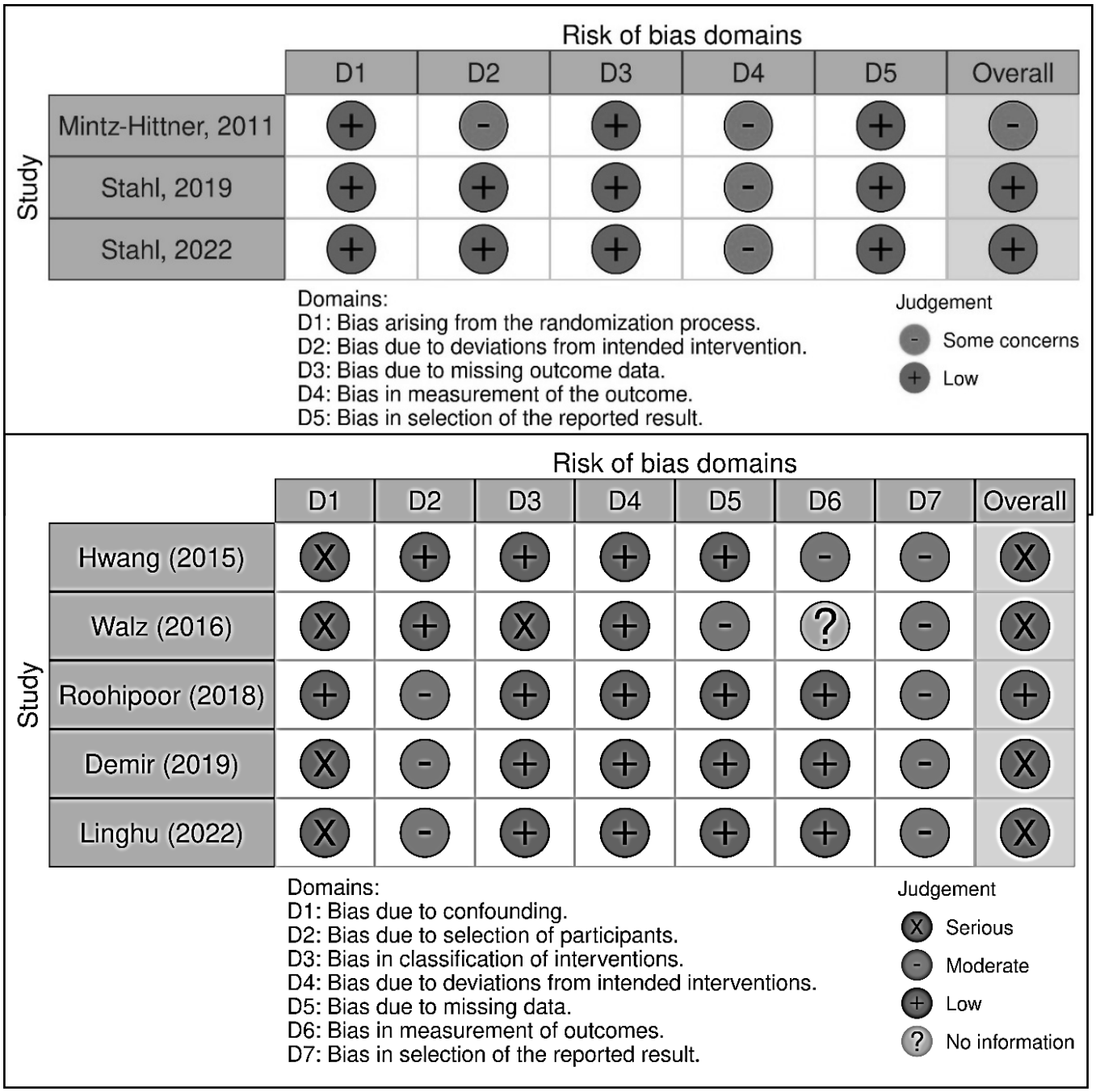

Figure 2: (Salim, Heriyanto, Elbert) Risk of bias assessment result for randomized controlled studies (above) and for non-randomized controlled studies (below).

received LPC in both zone 1 ROP (OR: 0.58; 95% CI: 0.33, 1.02; p = 0.06; I2: 81%) and zone 2 ROP (OR: 0.54; 95% CI: 0.21, 1.40; p= 0.21; I2: 0%), although the difference was not significant (Figure 5).

DISCUSSION

Our findings suggest that anti-VEGF therapy was more effective than LPC in achieving initial regression in Zone 1;in contrast, no significant differences were observed in Zone 2. Additionally, anti-VEGF treatment was associated with a lower recurrence rate, particularly in Zone 2, and fewer adverse structural outcomes compared to LPC. These findings highlighted the importance of considering the retinal zone in developing treatment strategies for ROP.

The anatomical division of ROP into zones, namely Zone 1, Zone 2, and Zone 3, serves as a cornerstone for therapeutic decision making.[12,20] Zone 1 disease carries a significantly high chance of worse prognosis due to its location at the posterior pole, because this region encompasses macula and fovea, which are indispensable for central vision, thus, the window for effective intervention is narrow. Consequently, immediate and precise management in Zone 1 is non-negotiable to avert permanent visual impairments.[1] In this high-risk region, our review indicated that anti-VEGF agents demonstrated superior efficacy. This performance could be attributable to the therapy's mechanism of action, the direct inhibition of the vascular endothelial growth factor, responsible for the pathological angiogenesis that precipitates retinal detachment and blindness in Zone 1.[7,20] The robust initial regression rates observed in our meta-analysis

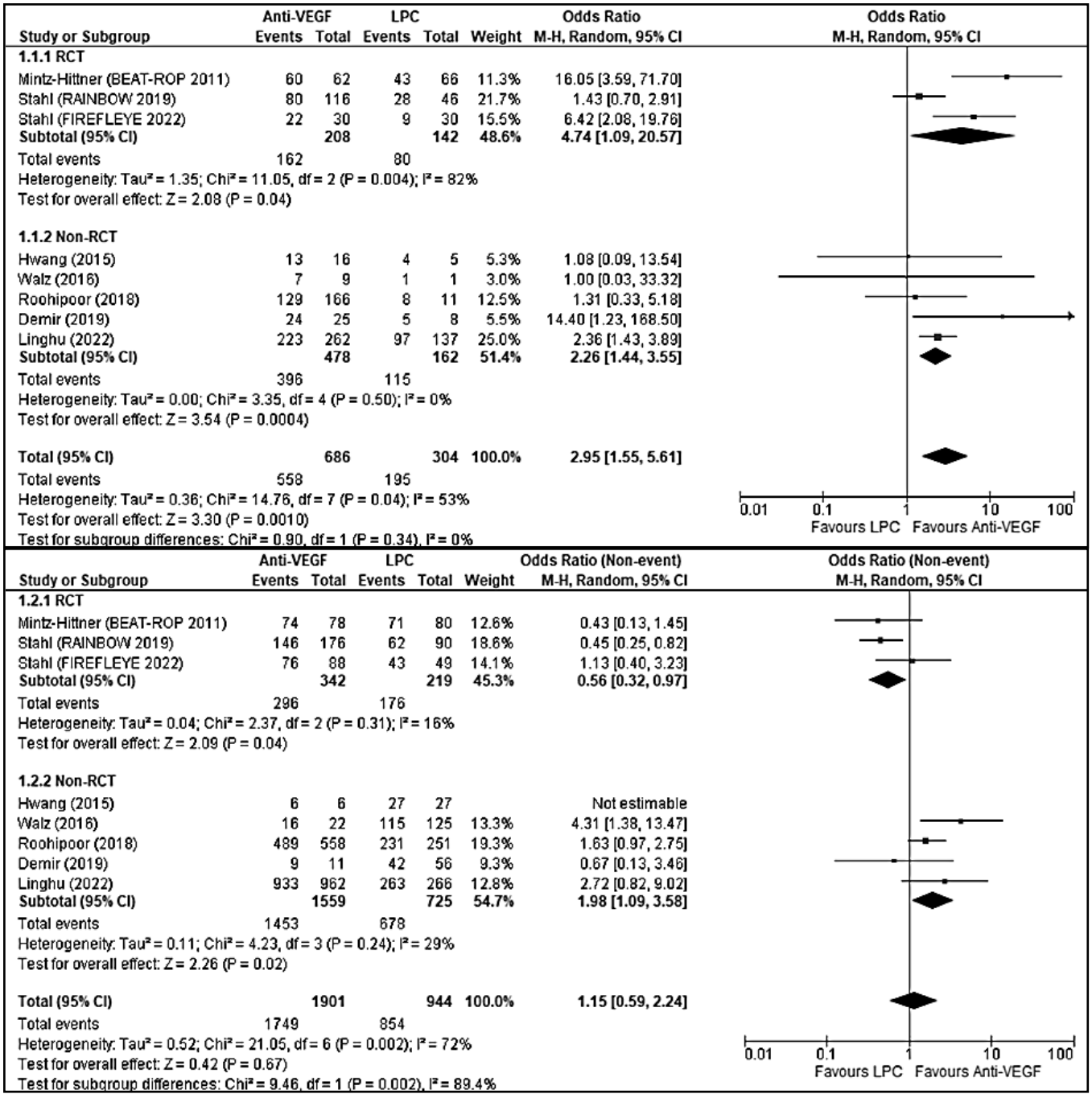

Figure 3: (Salim, Heriyanto, Elbert) Forest plot that demonstrates the initial regression in Zone 1 (above) and in 2 (below)

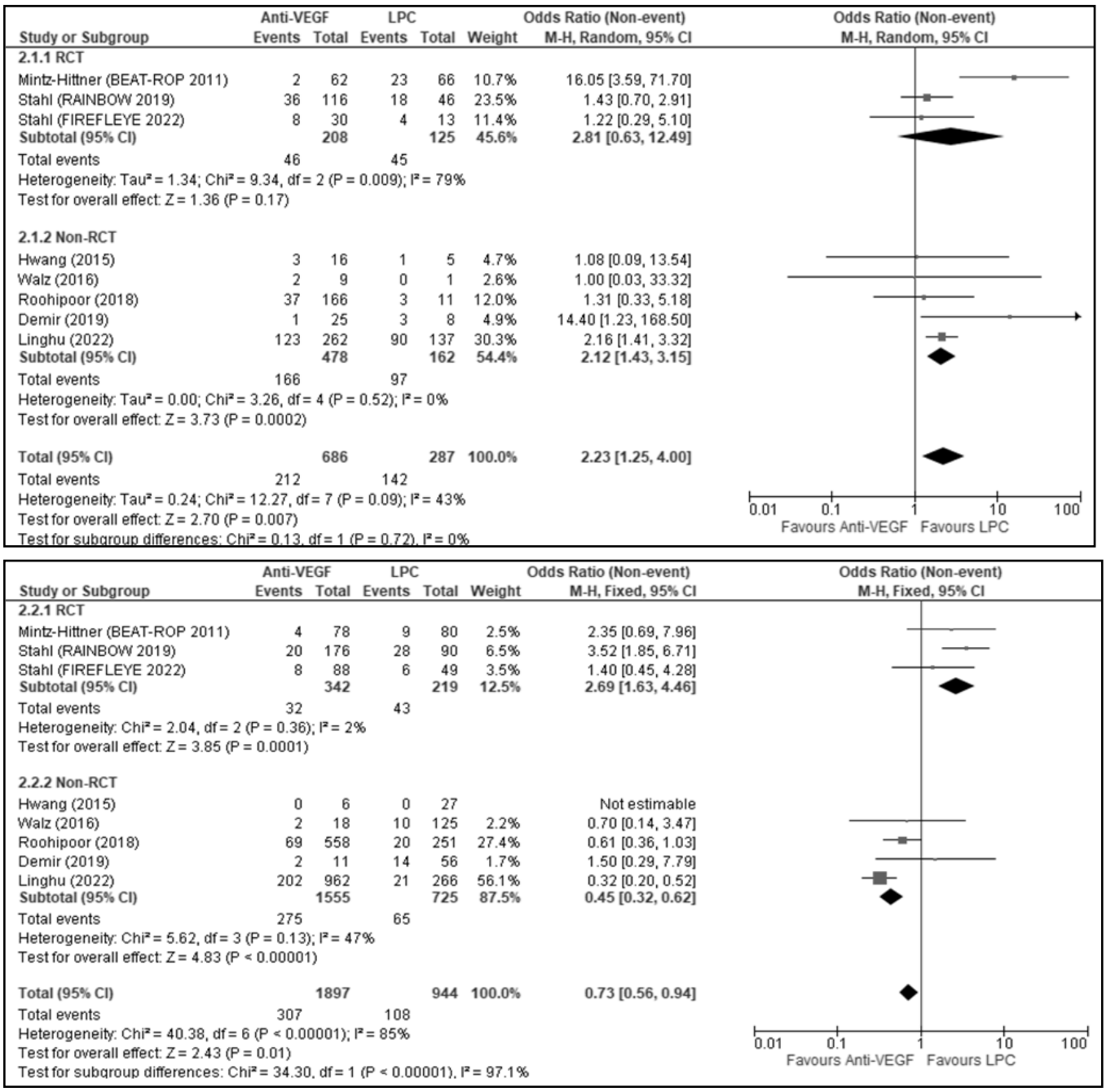

Figure 4: (Salim, Heriyanto, Elbert) Forest plot that demonstrates the recurrence in Zone 1 (above) and 2 (below).

underscore the value of positioning anti-VEGF as the primary intervention for these aggressive posterior cases.

Conversely, Zone 2 ROP presents a different clinical challenge.[6] While generally less severe than Zone 1, it affects a significantly larger surface area of the retina, presenting its own set of management difficulties.[21] Historically, LPC has been the standard, utilizing thermal ablation of the avascular retina to halt disease progression.[21–23] Our results suggested that within Zone 2, the disparity in initial regression rates between the two treatment was not statistically significant. This implies that for the broader, often less aggressive pathology found in Zone 2, laser therapy remains a scientifically justifiable and effective option.

Differentiating these zones provided a more personal, thus efficacious, treatment approach to ROP patients. For infants with Zone 1 ROP, where the risk

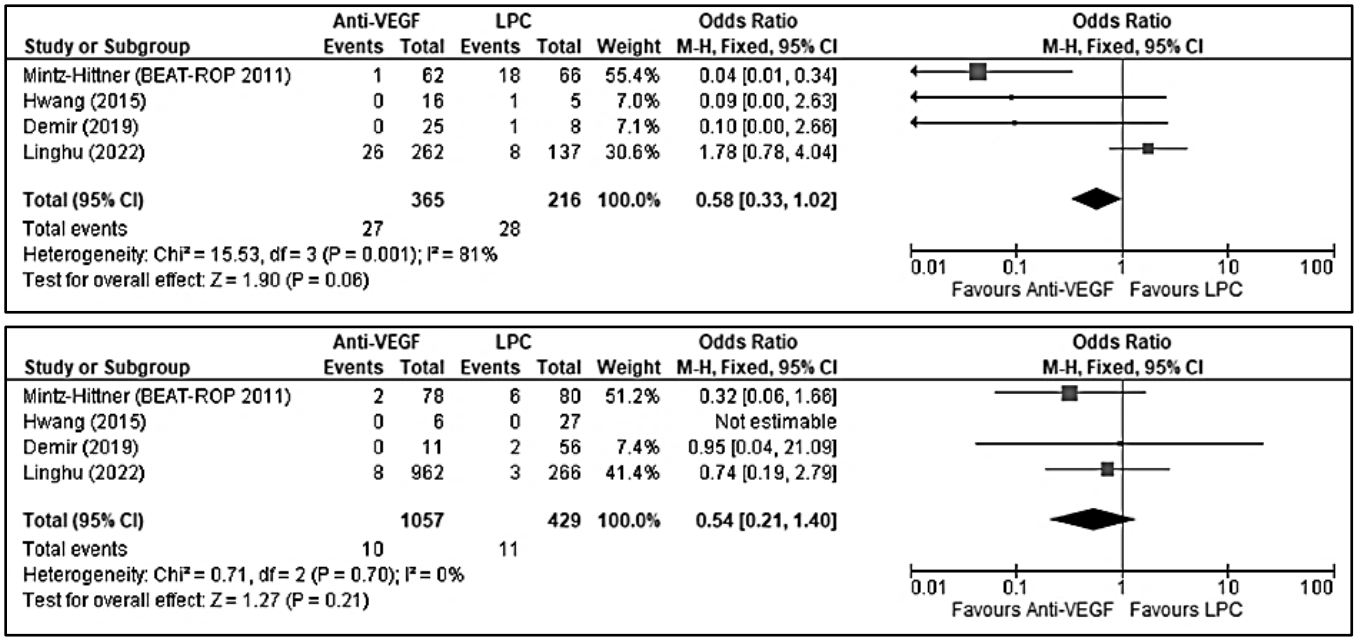

Figure 5: (Salim, Heriyanto, Elbert) Forest plot that demonstrates the unfavourable outcome in Zone 1(above) and 2 (below).

of severe outcomes is higher, prioritizing anti-VEGF to prevent regression and retinal complications could be the more popular choice. As for zone 2 ROP infants, laser therapy may be the better option, especially for those with a broader spread of pathology in retina.[1]

Additionally, the diminishing recurrence rates in Zone 2 through anti-VEGF therapy have their own clinical application. Laser therapy could be effective initially; however, due to its non-specific and invasive nature, recurrence is a possibility in zone 2. In contrast, a lower recurrence rate seen in anti-VEGF therapy could suggest that combination with laser treatment, or, in some cases, as an individual intervention, could be chosen to avoid the need for retreatment. This consideration is especially substantial in places where repeated laser therapy might be difficult or long-term follow-up of recurrences is warranted.[24]

Our meta-analysis results are like prior research that compared the effectiveness of anti-VEGF therapy with LPC in treating ROP.[25] Previous meta-analysis comparing anti-VEGF and LPC in type-1 and threshold ROP proved that laser was more effective than anti-VEGF. The study also found that LPC could cause more complications and worsen myopia in some cases, while anti-VEGF treatment was linked to fewer complications.[25] A recent study found that zone 1 ROP infants were more frequently treated with anti-VEGF, while zone 2 ROP infants with LPC. These findings suggest a tailored approach for each case based on the severity and zone of the ROP, with anti-VEGF therapy being favoured for aggressive types, and laser therapy for the less severe ones.[7]Furthermore, a network meta-analysis indicated that anti-VEGF agents might offer advantages in treating ROP, including a lower rate of retinal detachment, a higher spherical equivalent, and a lower occurrence of myopia compared to laser.[26] However, it also highlighted a higher retreatment rate with anti-VEGF therapy, suggesting the need for careful consideration in treatment planning. [26]

This study has some limitations. First, the study included varied sample sizes and the treatment for both anti-VEGF and laser photocoagulation, producing heterogeneity in the results. Although this problem was minimized by analysing the collective data into a forest plot that had considered heterogeneity and using random size effect, the possibility cannot be eliminated. Second, most of the included studies were retrospective, and some lacked external validation, raising questions about the real-world application. This problem was minimized using the risk of bias tools to exclude any studies that were determined to have high risk of bias. Third, the number of total events for unfavourable outcomes were minimal, potentially contributing to the insignificant difference found in the analysis. Prospective studies with larger sample sizes and in the form of clinical trials are warranted to better

understand the best treatment for each classification of ROP.

CONCLUSION

Our study show that compared to laser photocoagulation, anti-VEGF demonstrated superior initial regression in zone 1 but no discernible difference in zone 2. Reduced recurrence following initial therapy was seen in both zones 1 and 2. There was no discernible difference between the two groups' adverse results. To further understand the usage of anti-VEGF and laser photocoagulation for various zones in ROP, more clinical trials, and studies, including more samples, are necessary.

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Patient's Consent: Researchers followed the guidelines set forth in the Declaration of Helsinki.

Conflict of Interest: Authors declared no conflict of interest.

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Authors Designation and Contribution

Fatrin Patrycia Salim; Vitreoretina; Surgeon: *Concepts, Design, Literature Search, Data Analysis, Statistical Analysis, Manuscript Preparation, Manuscript Editing, Manuscript Review.*

Rivaldo Steven Heriyanto; Medical Doctor: *Concepts, Design, Literature Search, Data Acquisition, Data Analysis, Statistical Analysis, Manuscript Preparation, Manuscript Editing, Manuscript Review.*

Regan Elbert; Medical Doctor: *Concepts, Design, Data Acquisition, Data Analysis, Manuscript Preparation, Manuscript Editing, Manuscript Review.*