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Review Article

Evaluating the efficacy of pars plana vitrectomy in the management of endophthalmitis after following the endophthalmitis vitrectomy study: A systematic review and meta-analysis

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Abstract

Endophthalmitis is a devastating eye complication that requires prompt and effective treatment. A pivotal study in the field of endophthalmitis treatment is the endophthalmitis vitrectomy study (EVS), conducted over a decade ago. The primary objective of this study was to assess the effectiveness of pars plana vitrectomy (PPV) as a treatment option for endophthalmitis following the EVS study. We conducted a comprehensive search across three databases: PubMed, EBSCO host, and ProQuest. Reference lists of published articles were searched. Our study encompassed research conducted between January 2013 and January 2023 to ensure the most up-to-date findings. The best-corrected visual acuity (BCVA) in logMar, causative agents, and predicting factors for visual outcome were evaluated. Nine studies involving 351 eyes were included in the study; however, only eight were included in the meta-analysis. We observed a significant BCVA improvement compared to baseline at 1 month, >1–3 months, >3–6 months, and ≥12-month follow-up, with mean differences of 1.06 ($P < 0.001$), 1.25 ($P < 0.001$), 1.41 ($P < 0.001$), and 1.01 ($P < 0.001$), respectively. A causative organism was cultured in 61.4% of cases, and the majority of them were Coagulase-negative *Streptococcus*, *Staphylococcus aureus*, and *Streptococcus* sp. Factor associated with better visual acuity includes a younger age, lower intraocular pressure, and culture-negative endophthalmitis. Meanwhile, culture-positive endophthalmitis particularly *Streptococcus* sp., lower baseline vision, and presence of retinal detachment at initial presentation were identified as a prognostic for poorer visual outcome. PPV demonstrated a significant visual gain in patients with endophthalmitis in the 1st, 3rd, and 6th months. However, caution is warranted in drawing a definitive conclusion.

Keywords: *Endophthalmitis, Pars plana vitrectomy, Postoperative endophthalmitis*

Introduction

Endophthalmitis is an intraocular inflammation that may lead to severe visual loss or blindness. Typically endophthalmitis occur after several events such as penetrating trauma, ocular surgeries or injections, or endogenous spread [1]. The primary approach to treating endophthalmitis involves controlling infections, managing inflammation, and providing supportive care. Antibiotics are employed as a conservative treatment to control infections; meanwhile, the vitrectomy approach offers improvement of retinal oxygenation, reduces the inflammatory load and load of infection, offers specimens for diagnostic assessment, reduces disease severity, and accelerates visual rehabilitation [2].

The pivotal randomized controlled trial (RCT) addressing this matter is the endophthalmitis vitrectomy study (EVS), conducted in the early 1990s. The EVS demonstrated that pars plana vitrectomy (PPV) was beneficial for individuals with light perception (LP) vision at presentation. However, no additional advantages were observed when compared to intravitreal antibiotics alone for cases with hand movements (HM) or better vision [1-3].

It is important to note that in the EVS, PPV was defined as the removal of 50% vitreous using 20 G instrumentation.

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In current practice, micro-incision vitrectomy surgery employs 23 G and 25 G instrumentation for PPV. This technique, often sutureless, contributes to reduced surgical times compared to 20 G surgery. The use of 23 G and 25 G instrumentation not only minimizes intraoperative trauma but also lowers the incidence of complications, including retinal detachment, and diminishes postoperative inflammation and faster postoperative visual recovery. Enhancements in vitrectomy technology, including enhanced visualization facilitated by wide-angle viewing and smaller gauge instruments, could lead to a better visual outcome [1,3,4].

Although the EVS has significantly influenced treatment approaches, new clinical practices have emerged since the study's publication. Furthermore, it is crucial to recognize a notable limitation of the EVS, which exclusively focuses on postcataract surgery endophthalmitis, thus neglecting the exploration of other types of endophthalmitis [5].

Therefore, we aim to evaluate the efficacy of PPV for the treatment of endophthalmitis following the EVS study.

Methods

The systematic review has been officially registered in PROSPERO with the registration number CRD42023463927. Two independent reviewers MA and YS searched three electronic databases: PubMed, Proquest, and Ebsco with the keywords: "endophthalmitis," "postoperative endophthalmitis," "PPV," and " PPV," The search was limited to original studies, English language publications, and a time frame of 10 years to ensure the results remain current. The reference lists of selected articles were examined for additional publication.

Study selection

Full-text articles underwent a comprehensive review for potential inclusion based on the following criteria: (1) randomized controlled trials (RCTs), single-arm trials, cohort studies, case–control studies, case series, and cross-sectional studies were eligible. (2) Inclusion criteria encompassed patients experiencing acute endophthalmitis from any cause within a 6-week timeframe who underwent PPV. (3) The inclusion of best-corrected visual acuity (BCVA) measured in logMar as a continuous variable was required. In cases where multiple treatment arms were present, such as tap and inject and PPV, only studies involving PPV were considered. Studies were excluded if baseline or the outcome VA between tap and inject and PPV could not be distinguished and sample fewer than 20 eyes per treatment group.

Data selection, collection, and extraction

We employed the Mendeley reference manager to manage the identified studies. Initially, a deduplication procedure was done, followed by the evaluation of study titles and abstracts to determine eligibility. This evaluation was conducted independently by two co-authors. If studies were deemed potentially relevant during this preliminary assessment, a comprehensive full-text review was undertaken. In instances of disagreement during the selection or quality assessment phases, these matters were deliberated with two other co-authors to reach a consensus. Relevant data were extracted to perform a qualitative synthesis. The extracted data encompassed details such as author, year of publication, geographical locations, study designs, and inclusion and exclusion criteria. The primary outcome of this study is baseline, follow-up, and final VA. The secondary outcome was microorganism and prognostic factor of visual acuity (VA).

Quality assessment

The quality of cohort studies will be evaluated using the Newcastle–Ottawa Scale. For the case series studies, we use The Joanna Briggs Institute critical appraisal tool and ROBINS-I for nonrandomized clinical trial study.

Data analysis and synthesis

Our approach will involve qualitative synthesis, integrating data from both the textual content and tables across the included studies. This synthesis is aimed at providing a summary of the characteristics and findings of these studies. We will conduct meta-analyses using the random-effects model. The overall impact will assessed through the analysis of mean difference, along with a 95% confidence interval (CI). For the evaluation of statistical heterogeneity, the I^2 statistic will be employed. The data will be consolidated and computed using the statistical tool Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020. Oxford, UK.

Results

Study characteristics

A total of 1264 studies were identified through a combination of three databases and manual searching, as illustrated in Figure 1. After a thorough screening process, we included nine studies that investigated the efficacy of PPV and endophthalmitis. These nine studies consist of two nonrandomized controlled trials, two case series, four retrospective cohorts, and one single-arm clinical trial. Eight out of nine studies were included in the meta-analysis, whereas one study was excluded from the meta-analysis due to insufficient data. The participants' age ranged from 32 to 96 years old. Geographically, the distribution involved two studies conducted in the UK, two in the US, two in Iran, and the other three conducted in Australia, Hong Kong, and Germany. Across all studies, there were a cumulative 351 eyes included in the analysis. The cause of endophthalmitis varied: two studies exclusively focused on endophthalmitis due to intravitreal injection (IVI), three studies addressed postcataract endophthalmitis, and the remaining four included various causes of exogenous endophthalmitis such as posttrauma, post-PPV, bleb-related, posttrabeculectomy, and postintraocular lens change. For a comprehensive overview of study characteristics [Table 1].

Visual acuity outcomes

Data were pooled from eight studies, that evaluate the VA outcomes after PPV for endophthalmitis [6-13]. One study was excluded due to insufficient data, despite our attempts to contact the author. Mean changes in BCVA from baseline to specific postoperative intervals: 0–1 month, >1 month–3 months, >3 months–6 months, and ≥12-month post-PPV were examined.

The pooled data revealed a significant improvement in BCVA compared to baseline across various time frames:

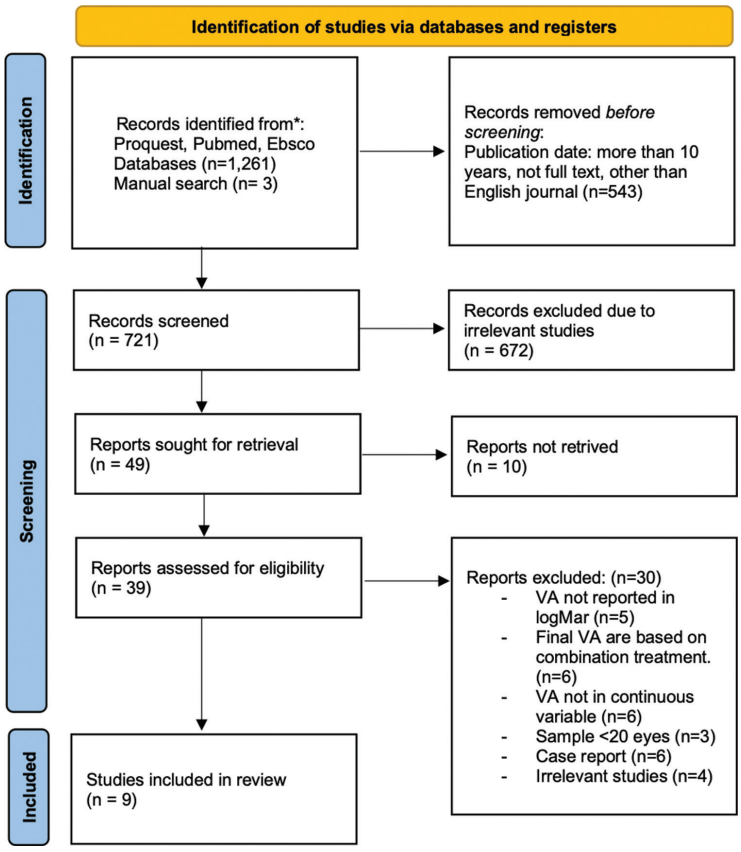

Figure 1: The PRISMA flow for this study

1.06 (95% CI, 0.90–1.21, $P < 0.001$) for 0–1 month, 1.25 (95% CI, 0.82–1.67, $P < 0.001$) for >1–3 months, 1.41 (95% CI, 0.82–1.67, $P < 0.001$) for >3–6 months, and 1.01 (95% CI, 0.86–1.17, $P < 0.001$) for ≥12 months [Figure 2].

In a subgroup analysis, we found BCVA gains within the first month were notable when PPV was conducted within 24 h 1.09 (95% CI, 0.97–1.21, $P < 0.001$). Meanwhile, PPV within 1 week also demonstrated a BCVA gain of 1.21 (95% CI, 0.31–2.12, $P = 0.009$) for 0–1 month, however, it did not reach statistical significance. Notable, over a ≥12-month follow-up, BCVA improvements persisted for both groups: 1.01 (95% CI, 0.83–1.19, $P < 0.001$) for PPV within 24 h and 1.04 (95% CI, 0.70–1.38, $P < 0.001$) for PPV within 1 week [Figure 2].

Meanwhile, in the EVS study, eyes with LP only-VA at presentation had a three times higher chance of reaching 20/40 vision with PPV compared with tap and inject (33% vs. 11%) [3].

Microbiology evaluation

The causative agents of endophthalmitis are shown in Table 2. A causative organism was cultured in 212/345 cases (61.4%) and the majority of them were *Coagulase-negative Staphylococcus* (79%) followed *by Staphylococcus aureus* (31.7%) and *Streptococcus* sp. (16.5%). In the EVS, 69.2% showed positive culture-positive cases, with 46.9% being *Coagulase-negative staphylococcus,* followed by other Gram-positive cases (15.5%), Gram-negative cases (4.1%), and polymicrobial infections (2.9%).

Factor that influenced the final visual acuity

Factors identified as positive prognostic indicators for final VA outcome include being a younger age (<85 years) [13], intraocular pressure (IOP) ≤25 mmgHg [13], cataract surgery as the cause of endophthalmitis [12,14], no growth in microbiology [7,8,12,14], having silicon-filled eyes [8], nondiabetic patients [8], and having Gram-positive as the causative agent [12].

On the contrary, adverse prognostic factors for the final VA include a poorer VA at baseline [6,13,14], the presence of retinal detachment at the time of presentation [10,13], undergoing glaucoma surgery compared to IVI or cataract surgery as the cause of endophthalmitis [6], a positive culture for *Streptococcus* sp. compared to coagulase-negative *Staphylococcus* [10,13], and positive microbial culture [13].

Risk of bias

All of the studies have minimal risk of bias [Supplementary Tables 1 and 2, Supplementary Figure 1].

Discussion

In our analysis, the mean changes in BCVA across distinct postoperative intervals revealed a consistent and time-dependent improvement compared to baseline. Specifically, at 0–1 month, >1–3 months, >3–6 months, and ≥12-month post-PPV, with the greatest mean observed at >3–6-month post-PPV (1.41). A sustained improvement was

Table 1: Characteristics of studies

Author (year)	Country	Study design	Mean age (SD)	Number eyes	PPV interval	Follow-up duration (months)	Treatment	Baseline BCVA (Log MAR)	Inclusion/exclusion criteria
Sousa *et al*., 2022 [12]	UK	Case series	76 (13.3)	41	1 (1–3 days)	1	Not mentioned	2.8 (1–2.8)	Inclusion: Acute endophthalmitis and treated with PPV within 7 days, min follow-up of 7 days Exclusion: Endogenous endophthalmitis, insufficient outcome
Ho *et al*., 2019 [14]	Australia	Retrospective cohort study	77.5 (36.2)	64	72 h	12	23 g 3 port PPV Tap and inject	3.1	Inclusion: Clinical diagnosis of microbial endophthalmitis, anterior chamber hypopyon and fibrin, loss of red reflex, and vitreous opacities
Xu *et al*., 2018 [13]	US	Nonrandomized interventional study	81.4	40	3.1 days (SD 1.4)	6	23 g (63.1%), 25 g (23.5%), 20 g (13.4%)	2.2	Inclusion: Presumptive endophthalmitis after anti-VEGF had occurred within 3 weeks after intravitreal injection Exclusion: Intravitreal injection other than anti-VEGF, history of intraocular or extraocular surgery, endophthalmitis posttrauma
Negretti *et al*., 2020 [11]	UK	Case series	63	27	Mean interval 7 days	18	23 g	2.17 (0.37)	Inclusion: Endophthalmitis cases that failed to improve following medical therapy or worsening vision despite medical therapy and proceeded to vitrectomy
Januschowski *et al*., 2021 [9]	Germany	Retrospective study	73 (31.11)	30	Within 6 h	14	23 g	1.66	Inclusion: Immediate vitrectomy <6 h Exclusion: Missing data
Tabatabaei *et al*., 2022 [8]	Iran	Nonrandomized controlled trial	64	23	Within 3 h	6	Not mentioned	2.4	Inclusion: Endophthalmitis due to uncomplicated phacoemulsification with clear cornea incision with HM VA Exclusion: Endophthalmitis due to other surgical procedures, history of prior visual loss, history of vitreoretinal surgery, other type of endophthalmitis
Najafabadi *et al*., 2023 [7]	Iran	Single arm clinical trial	63.8 (11.32)	27	Within 24 h	3	23 g	2.5 (0.46)	Inclusion: Exogenous endophthalmitis
Weber *et al*., 2023 [6]	USA	Retrospective cohort	76 (10.5)	82	Within 5 h	13.1	Not mentioned	2.1 (0.4–3.0)	Inclusion: Exogenous endophthalmitis
Iu *et al*., 2023 [10]	Hong Kong	Retrospective cohort	75.6 (43.0)	17	2 within 6 h, 10 within 24 h	20.2	Not mentioned	2.38 (0.19)	Inclusion: Acute postoperative endophthalmitis that developed within 6 weeks after cataract operation Exclusion: Chronic endophthalmitis (later than 6 weeks), combination with other intraocular surgery, other types of endophthalmitis (endogenous, posttraumatic, postintravitreal injection)

Anti-VEGF: Anti-vascular endothelial growth factor, BCVA: Best-corrected visual acuity, HM VA: Hand movement visual acuity, PPV: Pars plana vitrectomy, SD: Standard deviation, LogMAR: Logarithm of the minimum angle of resolution

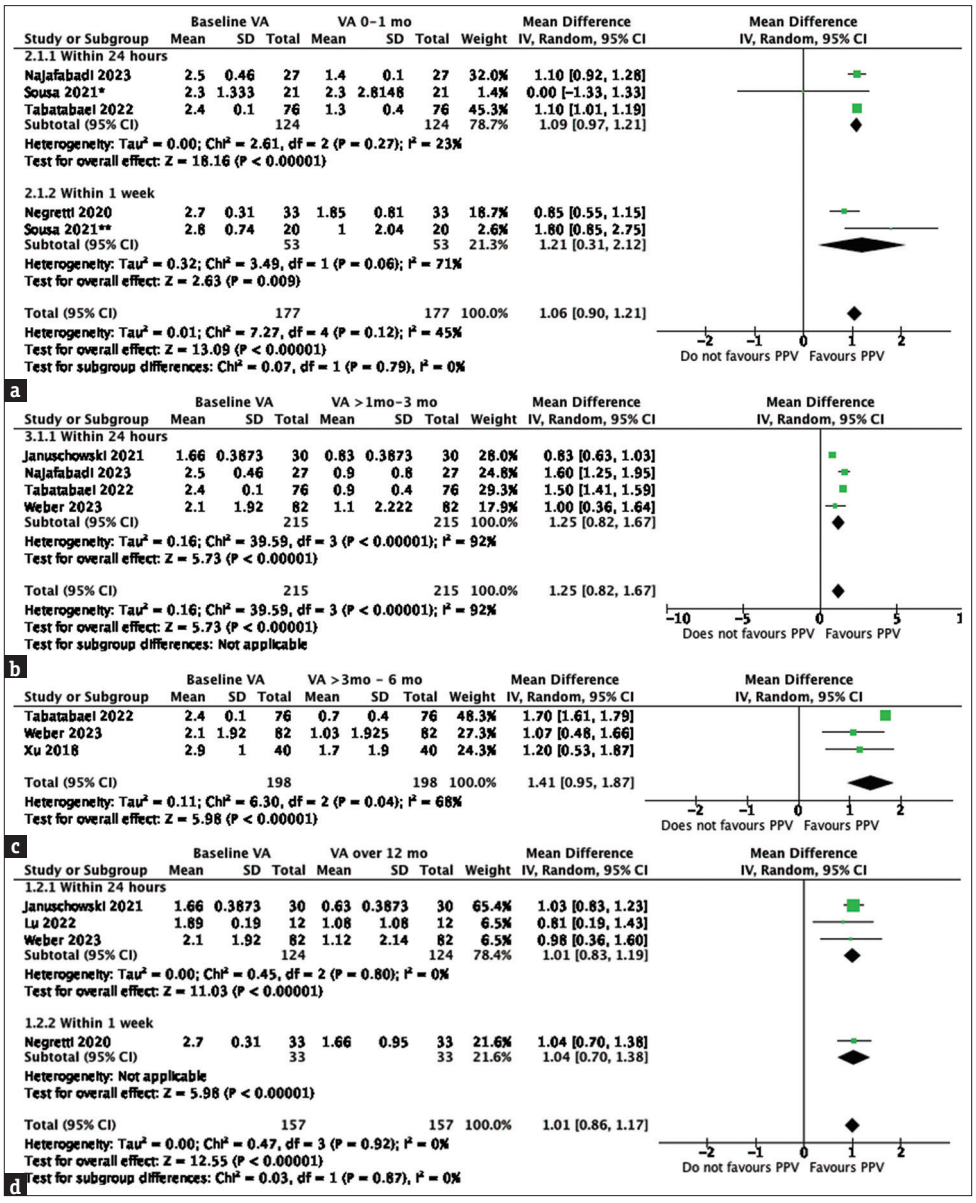

Figure 2: Mean change from baseline best-corrected visual acuity (BCVA) in eyes treated with pars plana vitrectomy. (a) Overall mean BCVA change from baseline to 1 month. (b) Overall mean BCVA changes from baseline to >1 month–3 months. (c) Overall mean BCVA change from baseline to >3 months–6 months. (d) Overall mean BCVA change from baseline to ≥12 months. CI: Confidence interval, SD: Standard deviation, PPV: Pars plana vitrectomy, VA: Visual acuity

observed even at the extended follow-up of ≥12 months (1.01). This may demonstrate a positive impact of PPV on visual outcomes over the long term.

Notably, these BCVA gains within the 1st month were particularly significant when PPV was conducted within 24 h. This might show a potential benefit of early surgical intervention, suggesting a prompt response may contribute to accelerated visual recovery in the initial stages post-PPV. BCVA improvements persist at the ≥12-month follow-up for both subgroups, within 24 h and 1 week.

There remains a debate regarding the optimal timing of PPV. Early PPV, performed within 24 h of presentation, allows prompt removal of infective and inflammatory load in the vitreous, thereby reducing further inflammatory damage to the retina. The EVS mandated immediate vitrectomy within 6 h of presentation, which may not be feasible in clinical settings [15-17]. Meanwhile, another study suggests that the outcomes of early PPV may not be as favorable as an immediate vitreous tap and intravitreal antibiotics injections, followed by a semi-urgent PPV. This is because antibiotics ideally should be administered immediately, before the plateau phase to reduce retinal damage induced by bacterial toxins and inflammatory load. In addition, there is a limited potential for iatrogenic complications possibly associated with early surgery in certain cases [12]. Ultimately, surveys of ophthalmologists have found majority perform early PPV in cases where clinical deterioration within 48 h following tap and inject [15].

Table 2: Causative microorganisms in endophthalmitis

Study (years)	Number of cases	Culture negative, *n* (%)	Culture positive, *n* (%)	*Staphylococcus aureus*, *n* (%)	Coagulase-negative staphylococci, *n* (%)	*Enterococcus* sp, *n* (%)	*Streptococcus* sp, *n* (%)	Gram-negative, *n* (%)	Fungi, *n* (%)
Sousa *et al*., (2022) [12]	41	16 (39)	25 (61)	-	13 (52)	2 (8)	6 (24)	3 (12)	1 (4)
Negretti *et al*,. (2020)[11]	27	6 (22)	21 (78)	5 (24)	1 (4.7)	1 (4.7)	5 (23.8)	8 (38)	1 (4.7)
Januschowski *et al*., 2021[9]	29	8 (27.5)	21 (72.5)	1 (4.7)	19 (90.5)	-	-	1 (4.7)	-
Tabatabaci *et al*., 2022[8]	23	8 (34.8)	15 (65.2)	5 (21.7)	9 (39.1)	-	1 (4.3)	-	-
Najafabadi *et al*., 2023[7]	27	9 (33)	18 (79)	11 (55.5)	-	-	-	-	-
Xu *et al*., 2018[13]	40	16 (40)	24 (60)	-	16 (66.7)	-	4 (10)	2 (8.3)	-
Iu *et al*., 2023[10]	12	1 (8.3)	11 (91.7)	1 (9)	3 (27.3)	3 (27.3)	2 (18)	2 (18)	-
Ho *et al*., 2019[14]	64	20 (31)	42 (66)	5 (12)	18 (43)	2 (5)	14 (33)	3 (7)	-
Weber *et al*., 2023[26]	82	47 (57.3)	35 (74.4)	8 (9.8)	22 (62.8)	-	3 (8.7)	2 (5.7)	-

The EVS demonstrated that PPV was beneficial for individuals with LP vision at presentation with no advantages for cases with HM or better [3]. However, Ho *et al*. observed that patients with baseline VA of LP and HM experienced similar visual improvements, suggesting that early PPV might offer benefits not only for LP vision. Consequently, a clinical trial regarding this area is warranted [14].

The positive culture rate was 61.4% in this study, which was lower than observed in the EVS (69%). Most culture-positive cases in our study are Coagulase-negative *Staphylococcus*, *S. aureus*, and *Streptococcus* sp. as the predominant causative agents. This finding is in line with the EVS results indicating a 70% prevalence of coagulase-negative *Staphylococcus* in cultured-positive cases, which constitute normal flora of human skin [3]. This demonstrated the importance of proper aseptic technique to prevent endophthalmitis postocular surgery or injection. Notably, topical povidone-iodine stands as the sole proven prophylaxis against endophthalmitis, emphasizing the need for its application before using viscous anesthetic agents, which may hinder povidone-iodine's efficacy by forming a barrier [18-21].

The *Streptococcus*-associated postoperative endophthalmitis rate was 9.0% in EVS [3], with previous studies indicating higher proportions (30.9% and 24.4%) after anti-VEGF injection [20,22]. This suggests a shifting spectrum of organisms between clinical and operating room settings, with *Streptococcus* species emerging as a more prevalent cause post-IVI. The elevated *Streptococcus* incidence may be linked to potential aerosol contamination from respiratory flora, highlighting the importance of measures such as restricting patient and provider communication during the procedure to minimize infection risk [20,23,24] or applying povidone-iodine after placement of the lid speculum [25].

Our study demonstrated that culture-positive agents especially *Streptococcal* sp. as the causative agents associated with poorer outcomes, this might be because culture-positive cases may suggest more virulent bacteria and higher intraocular bacterial load. Studies indicate that *Staphylococcus epidermidis*, as the causative agent of culture-positive endophthalmitis, may be associated with a better visual outcome compared to other pathogens. In addition, Gram-positive organisms, especially *Streptococcal* sp. are linked to worse visual outcomes, possibly due to their virulence causing severe inflammation and tissue damage, limiting chances for improvement even with vitrectomy [26-29].

Our study shows that a lower baseline of VA is a worse prognostic factor. This result was in line with the previous studies, highlighting the association between visual outcomes and initial VA, with poorer VA and retinal detachment predicting unfavorable outcome (odds ratio; 12.2 and 7.7, respectively) [13,26]. In EVS, patients with a presenting IOP >25 mmHg were 1.4 times more likely to experience a decrease in vision compared with those with an IOP between 5 and 25 IOP mmHg [3]. Meanwhile, in Xu *et al*., the IOP >25 mmHg was 40.8 times (95% CI, 2.1–92.5) less likely to achieve a BCVA of 20/400 or better at the 6-month follow-up compared to those with presenting IOP 5 and 25 mmHg. This possibly reflects increased inflammation or contributing to existing optic neuropathy [13].

This study faces limitations, primarily due to the most of the included studies were case series or retrospective studies, which lowers the overall quality of evidence and makes it susceptible to biases. Furthermore, the research exhibits heterogeneity, due to the inclusion of varied causes of endophthalmitis, including postcataract, IVI, ocular trauma, and others. This variation in etiology may introduce bias, as each source of endophthalmitis could involve different mechanisms, microbial causes, and treatment responses. In addition, our research encountered differences in the selection of PPV treatments, and differences in surgeon skills that may impact surgical outcomes. Furthermore, the difference in durations of follow-up may have an impact on the final vision. From a geographic perspective, while two papers from Iran were included, there was a notable absence of papers

from East and South Asia such as Japan, Korea, and India. This lack of representation from key regions may impact the generalizability of the findings. Considering the findings from both this and earlier studies, it is possible to guide an additional RCT that specifically examines the effectiveness of PPV based on the visual presentation and the cause of endophthalmitis.

Conclusion

PPV demonstrated significant visual improvement in patients with endophthalmitis in the first, third, and 6th months. However, caution is warranted in drawing a definitive conclusion. Additional studies are necessary to establish a comprehensive understanding of this outcome.

Data availability statement

The datasets generated during and/or analyzed during the current study are available in the FigShare repository, entitled PPV for endophthalmitis, DOI 10.6084/m9.figshare.25397257.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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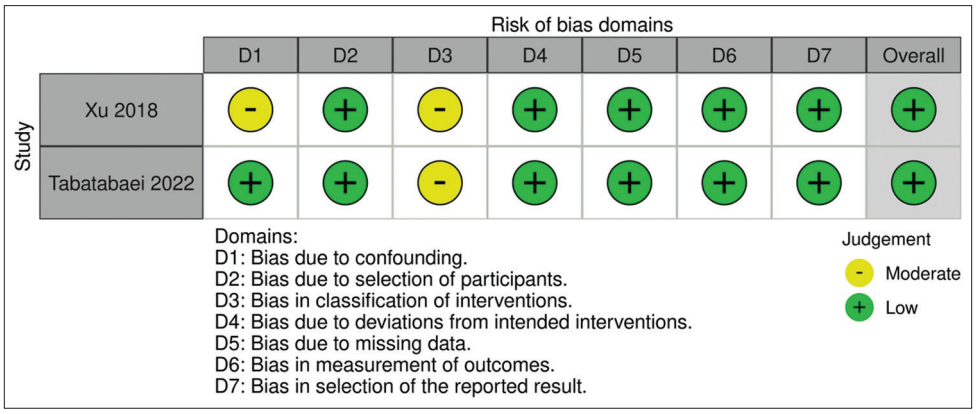
Supplementary Table 1: Risk of Bias Cohort Studies using Newcastle–Ottawa Scale

Studies	Selection	Comparability	Outcome	Total
Ho *et al*., 2019 [14]	****	*	***	8/9
Januschowski *et al*., 2021 [9]	****	*	***	8/9
Ho *et al*., 2023 [10]	****	*	***	8/9
Weber *et al*., 2023 [6]	****	*	***	8/9

*1 point, ***3 points, ****4 points

Supplementary Table 2: Risk of bias case series studies using Joanna Briggs Institute's critical appraisal tools

JBI checklist questions	Sousa *et al*., 2022	Negretti *et al*., 2020
Were there clear criteria for inclusion in the case series?	Yes	Yes
Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes	Yes
Were valid methods used for the identification of the condition for all participants included in the case series?	Yes	Yes
Did the case series have consecutive inclusion of participants?	Yes	Yes
Was there clear reporting of the demographics of the participants in the study?	Yes	No
Was there clear reporting of clinical information of the participants?	No	No
Were the outcomes of follow-up results of cases clearly reported?	Yes	Yes
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	No	No
Was statistical analysis appropriate?	Yes	Yes



Supplementary Figure 1: Risk of bias of nonrandomized clinical trial studies with ROBINS-I tool