# Evaluating the Safety and Efficacy of Ocriplasmin in Pediatric Versus Adult Ophthalmology: A Systematic Review and Meta-Analysis

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**KEYWORDS**
Ocriplasmin, Pediatric Ophthalmology, Posterior Vitreous Detachment (PVD), Vitreomacular adhesion, Vitreoretinal traction syndrome, Vitrectomy surgery

**ABSTRACT**
**Introduction:** This study assessed the safety and efficacy of ocriplasmin in pediatric ophthalmology, focusing primarily on pediatric patients. It also considered adult cases to address specific aspects of its safety and effectiveness.**Methods:** This systematic literature review was conducted following the PRISMA guidelines, incorporating 15 articles that included 901 cases in the ocriplasmin group and 529 cases in the ALG-1001 group within pediatric populations. The review compared the effectiveness and safety of ocriplasmin in pediatric ophthalmology to that of ALG-1001, focusing on outcomes such as vitreomacular adhesion (VMA) release, macular hole (MH) closure, and vitreomacular traction (VMT) release.
**Results:** The study findings revealed that ocriplasmin demonstrated a higher MH closure rate (OR=3.16; 95% CI: 1.29-7.42; P=0.044) compared to ALG-1001. Additionally, ocriplasmin had a higher VMA release rate (OR=2.92; 95% CI: 1.31-7.52; P=0.022) and VMT release rate (OR=3.51; 95% CI: 1.43-7.13; P=0.002). There were no complications associated with ocriplasmin use among pediatric patients.
**Conclusion:** This meta-analysis affirms ocriplasmin's safety and efficacy in pediatric ophthalmology, surpassing ALG-1001 for VMT, MH, and VMA. Despite the limitations in existing literature, ocriplasmin proves more effective, indicating potential clinical utility for challenging cases with strong adhering Posterior Vitreous Detachment (PVD), where vitrectomy is difficult.

## 1. Introduction

Ocriplasmin is adopted in ophthalmology for treating certain eye conditions relating to the vitreomacular interface, such as macular holes (MH), vitreomacular traction (VMT), and symptomatic vitreomacular adhesion (VMA) [1, 2]. This medication induces enzymatic vitreolysis and breaks down specific proteins, mainly laminin and fibronectin, responsible for the adhesion between the eye macula and the vitreous gel [3]. By enzymatically breaking down these proteins, ocriplasmin helps release abnormal vitreous adhesions, making it possible for the vitreous gel to separate from the macula [4, 5]. This drug can be used as a pharmacological alternative to surgical intervention, especially in vitrectomy in cases where small MH or symptomatic VMA are present [6, 7-9]. Also, it can be used at a stage before the surgical intervention, especially if the adhesion is too persistent. This pre-treatment can facilitate a smoother vitrectomy in particularly challenging cases. It is important to note that ocriplasmin, though previously considered a potential agent for vitreolysis in pediatric patients, requires careful consideration due to its specific effects and outcomes. Understanding the role of

ocriplasmin in pediatric vitreolysis can help optimize its use and improve surgical outcomes [10], but has recently been overshadowed by emergent safer and more effective alternatives owing to the associated adverse effects [11].

The adverse effects of ocriplasmin include eye pain, visual disturbances, retinal tears, and visual disturbances [11-13]. A resolution to use ocriplasmin is reached after carefully considering its benefits versus risks depending on the patient's specific requirements [1,6]. The utilization of ocriplasmin in pediatric ophthalmology presents a notable advancement in treating and managing certain vitreomacular interface disorders [14-18]. However, ongoing research is actively refining the application criteria for ocriplasmin, with a strong emphasis on improving its efficacy and safety across various patient populations. Understanding the adverse effects associated with ocriplasmin in pediatric care is crucial, given the delicate nature of this population [19-23]. Zhang *et al*. [4] noted that ocriplasmin while presenting a significant advancement in treating vitreomacular interface disorders, requires a nuanced approach to its use. Specific to the pediatric population, ocular complications such as visual disturbances and retinal tears require careful evaluation and monitoring [7, 24, 25].

The decision-making process for using ocriplasmin in pediatric cases involves carefully weighing the anticipated therapeutic benefits against the potential risks and adverse effects. This requires considering the unique vulnerabilities and developmental aspects of young patients. Physicians must evaluate how ocriplasmin may affect the developing eyes of children, balancing the advantages, such as improved surgical outcomes, with the potential for adverse effects. Ensuring the treatment enhances patient outcomes without compromising safety is crucial. By focusing on these critical factors, healthcare providers can make informed decisions that prioritize the well-being of young patients [26-28]. This is because ocriplasmin has raised significant concerns regarding its efficacy and safety in clinical practice, leading to the development and exploration of alternative treatment modalities. Studies evaluating the efficacy of hyaloid and ocriplasmin in pediatric vitreolysis have shown inconsistent results. Some studies indicate positive outcomes, while others highlight potential risks and limited effectiveness. These mixed findings underscore the need for continued research to determine the most reliable and safe treatments. By investigating alternative approaches, healthcare providers aim to improve patient outcomes and reduce potential complications in pediatric vitreolysis. These mixed findings underscore the need for further research to determine the most reliable and safe treatment options for pediatric patients. Studies evaluating the efficacy of hyaloid and ocriplasmin in pediatric vitreolysis have shown inconsistent results [11,13, 29-32]. While some cases reported successful resolution of vitreoretinal adhesions, others showed minimal improvement or even exacerbation of the condition [14,33]. This inconsistency in outcomes raised doubts about the reliability of these agents in pediatric cases. Safety is a paramount concern, especially in pediatrics. Both hyaloid and ocriplasmin have been associated with adverse effects, including intraocular inflammation, retinal detachment, and subretinal hemorrhage [34, 35]. These adverse events, particularly in young patients, raised significant concerns among clinicians regarding the safety profile of these agents [14, 34]. The emergence of alternative treatments with better efficacy and safety profiles has diminished the relevance of hyaloid and ocriplasmin in pediatric vitreolysis. These new and advanced treatments offer enhanced therapeutic outcomes and reduced risk profiles, making them more appropriate for managing vitreous conditions in pediatric patients. Surgical techniques such as pars plana vitrectomy (PPV) have become the standard for conditions like PFV and VMT [36-38]. PPV allows for the precise removal of vitreous adhesions under direct visualization, offering better control and outcomes than pharmacologic agents like hyaloid and ocriplasmin [34].

This research focuses on the efficacy and safety of ocriplasmin in achieving the intended therapeutic outcomes among the pediatric age group. Given that ocriplasmin has faced

the challenge of becoming obsolete, it is imperative to consider the alternative allegro ALG-1001. ALG-1001 is a novel RGD-class oligopeptide that functions as an integrin receptor inhibitor, playing a role in preventing angiogenesis. This synthetic oligopeptide, composed of arginine-glycine-aspartic acid, interacts with several integrin receptor sites. By targeting integrin receptors, ALG-1001 impacts cell signaling, regulation, and the formation of new and abnormal blood vessels. It employs two unique mechanisms, antiangiogenesis and vitreolysis, which make it effective in treating various vitreoretinal conditions. Whereas ocriplasmin may not address vitreolysis concerns, considering the contributions of the allegro Ophthalmics' ALG-1001 is essential. ALG-1001 is a synthetic peptide that targets and inhibits the integrin receptor αvβ3 and is involved in cellular processes critical in the pathogenesis of various ocular diseases [39]. Both ALG-1001 and ocriplasmin are beneficial in managing pediatric vitreoretinal disorders. While ALG-1001 targets integrin receptors involved in fibrosis and angiogenesis, ocriplasmin acts on vitreoretinal adhesion proteins [40].

This study assessed the safety and efficacy of ocriplasmin in pediatric ophthalmology, with a primary focus on pediatric patients and considering adult cases to address specific aspects of its safety and efficacy. The review was guided by the following research questions to achieve this objective: 1) Is ocriplasmin safe and effective for pediatric patients, given concerns about the intervention being obsolete? 2) What are the common vitreolysis concerns associated with ocriplasmin use among pediatric patients? 3) How does the safety and effectiveness of ocriplasmin compare with other drugs used for the same roles, such as ALG-1001? 4) As ocriplasmin is considered a weak medication (50% success rate), is this medication dosage useful for pediatric patients and appropriate for disrupting the tight adhesion between the vitreous humor and retina?

## 2. Methods

### 2.1. *Search Strategy*

This systematic review of literature adopted the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines. The researchers searched for studies that used ocriplasmin for treating certain eye conditions relating to the vitreomacular interface, such as MH, VMT, and VMA among pediatric patients. The PubMed/MEDLINE, CINAHL, Scopus, Embase, PsycINFO, and Web of Science databases were systematically searched for all sources, including relevant information on the safety and efficacy of ocriplasmin in pediatric ophthalmology. The terms adopted for the systematic search included ocriplasmin, ocriplasmin use in pediatric ophthalmology, pediatric ophthalmology, posterior vitreous detachment (PVD) vitreomacular adhesion, vitreoretinal traction syndrome, vitrectomy surgery, ocular complications, safety, and efficacy. The following criteria for inclusion and exclusion were used in the process of screening articles:

### 2.2 *Inclusion and Exclusion Criteria*

This review only incorporated articles that met all the criteria mentioned below:

1. Studies involving pediatric and or adult patients receiving ocriplasmin to ease the process of vitrectomy or prevent vitreomacular adhesion or related conditions.
2. Studies focused on the efficacy and safety of ocriplasmin in pediatric and or adult patients.
3. Studies published within the past ten years (2013-2023).

The following studies were excluded from the study:

1. Studies without sufficient data on the safety and efficacy of ocriplasmin.
2. Studies published before 2013.

### 2.3 *Article Screening Process*

All articles obtained from the literature search were initially screened based on the title and abstract to determine eligibility. It was followed by a thorough review of the complete article to assess their suitability in answering the research questions. All the sources acquired using the search terms were primarily filtered as open-access research articles, with studies

focusing on the safety, efficacy, and complications associated with ocriplasmin use among pediatric patients. The sources obtained from the literature search were analyzed per the patient/population, intervention, comparison, and outcomes (PICO) format below:
Population: Pediatric patients (6-12 years)
Intervention: Administration of ocriplasmin
Comparison: Comparing the population exposed to Ocriplasmin against the control group with respect to complications such as eye redness, dry eye, eye floaters, eye hemorrhage, eye discomfort, and complexity in vitrectomy surgery.
Outcome: Efficacy, safety profile, occurrence of complications, and complexity in performing vitrectomy surgery.

### 2.4 *Risk of Bias Analysis*

The Cochrane risk of bias tool for randomized trials (RoB 2) was used to analyze retrieved sources through R programming. The analysis was conducted based on the possible domains of bias, including bias arising from intended intervention, from the randomization process, due to missing data, in measuring the outcome, and in selecting the reported result.

### 2.5 *Meta-Analysis*

The RevMan 5.3 software was accessed from the Cochrane Collaboration to conduct the statistical analysis. Standard deviations (SDs) and means were used to calculate the weighted mean differences with 95% confidence intervals (C1). For all the dichotomous outcomes, odds ratios (ORs) were calculated for 95% CI. A chi-square ($X^2$) test was conducted to assess the statistical heterogeneity between the included articles. The random-effects model was employed for cases where $P< 0.05$ and $I^2 >50\%$. However, in the event $I^2 \leq 50\%$, the fixed-effects model was used in data analysis since heterogeneity was considered low.

## 3. Results

### 3.1. *Study Selection*

The initial search resulted in 126 articles from five electronic databases, including PubMed/MEDLINE (35), Embase (13), CINAHL (34), Scopus (15), PsycINFO (23), and Web of Science (6) databases. A total of 55 sources were left for further analysis after reviews, case reports, duplications, and other articles marked as ineligible by automation tools were excluded from the analysis. The sources were subjected to further screening by applying the aforementioned inclusion and exclusion criteria. A total of 45 sources that did not focus on the safety and efficacy of ocriplasmin in pediatric ophthalmology and lacked sufficient data on the same in pediatric patients were removed from the analysis. The researcher remained with a total of 15 articles that were utilized in the study. The article selection process has been presented as a PRISMA flow diagram (Fig. **1**), as shown below.

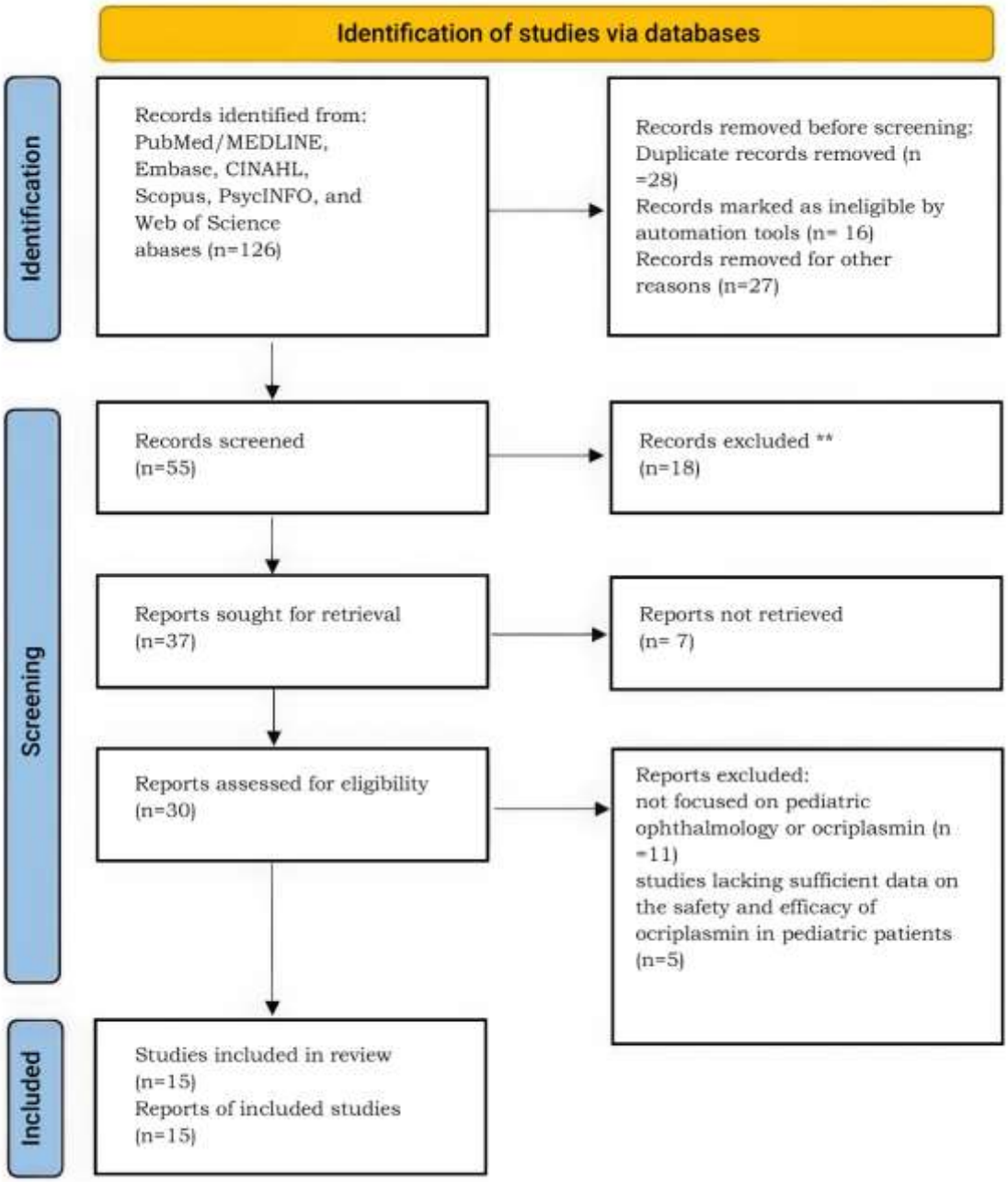



**Fig. (1).** PRISMA flow diagram of systematic review.

### 3.2. *Study Characteristics*

Table 1 details the primary attributes of the studies incorporated in this systematic review. This review comprises 15 pertinent research articles published between 2013 and 2023. The studies incorporated in this review represented pediatric and or adult patients with VMT, MH, and VMA. The efficacy and safety of ocriplasmin in pediatric ophthalmology were compared with ALG-1001 (another drug used for the same roles) with regard to VMA release, MH closure, and VMT release. The mean age of the population included in this review was 29.2 years. The geographic locations of the considered studies included the United States, China, Canada, the United Kingdom, and India. All the pediatric patients included in this meta-analysis were scheduled to undergo vitrectomy for either VMT, MH, or VMA.

Table **1**. Characteristics of the Studies Included in the Review.

| Reference | Study Type | Population | Intervention | Comparison | Findings |
|---|---|---|---|---|---|
| Zhang *et al* [4] | Systematic review and meta-analysis | vitreous macular traction (VMT) patients younger than 65 years | Ocriplasmin administration | Control group | Ocriplasmin is an effective, reliable, and relatively safe intervention for the treatment of VMT among patients younger than 65 years |
| Drenser *et al* [41] | Clinical trial | 22 pediatric patients scheduled for vitrectomy | Ocriplasmin administration | Control group | Pediatric patients tolerated an intravitreal injection of 175 µg of ocriplasmin before undergoing vitrectomy. |
| Wong, SC & Capone Jr [42] | Systematic review | pediatric patients scheduled for vitrectomy | Ocriplasmin administration | Control group | Ocriplasmin stands as a potential alternative to autologous plasmin enzyme in aiding vitrectomy surgeries. |
| Chang and MIC Study Group [43] | Clinical trial | 43 pediatric vitrectomy candidates 16 years or younger | Ocriplasmin administration | Control group | Ocriplasmin stands as a potential alternative to adjunct to vitrectomy for the treatment of pediatric patients. |
| Kaiser *et al* [44] | Clinical trial | 71 patients with symptomatic vitreomacular adhesion | Ocriplasmin administration | Control group | ocriplasmin injection provides a generally well-tolerated pharmacologic |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | treatment option for patients with symptomatic vitreomacular adhesion/ |
| Morescalchi *et al* [34] | Systematic review and meta-analysis | patients with symptomatic vitreomacular adhesion | Ocriplasmin administration | Control group | The prevalence of adverse events (OAEs) of ocriplasmin is very low but on rare occasions, can result in retinal dysfunction |
| Nudleman and Capone [45] | Systematic review and meta-analysis | Children with complicated vitreoretinopathies. | Ocriplasmin administration | Control group | The use of ocriplasmin in young children lowers the risk of creating an iatrogenic retinal break during membrane peeling |

| | | | | | |
|---|---|---|---|---|---|
| Vasquez *et al* [39] | A single-center retrospective chart review study | patients who underwent primary 25-gauge vitrectomy for symptomatic vitreomacular traction. | Ocriplasmin administration | Control group | ocriplasmin is safe and effective in patients meeting the following criteria: a) presence of native lens, b) absence of epiretinal membrane and c) macular hole (MH) less than 400 μm in diameter. ocriplasmin is safe and cost effective when used for managing VMT |
| Bormann *et al* [46] | a retrospective analysis | 10 patients with VMT | Ocriplasmin administration | Control group | The adoption of ocriplasmin showed a 70% effectiveness in the resolution of VMT |
| Khanani *et al* [47] | observational study | Patients with symptomatic VMA/VMT were treated with ocriplasmin. | intravitreal injection of ocriplasmin | Control group | the use of ocriplasmin treatment proves effective and well-tolerated among patients with VMT |
| Haller *et al* [48] | Randomized, placebo-controlled studies | patients with VMA/ VMT | intravitreal injection of ocriplasmin | Control group | Ocriplasmin was more effective in younger patients (<65 years). This drug has a positive effect |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | across all populations |
| Barca *et al* [49] | An observational retrospective multicentre study | Patients with symptomatic distortion and loss of vision secondary to VMT | Ocriplasmin administration | Control group | Ocriplasmin has a good safety profile and can serve as a potential alternative treatment for patients with symptomatic VMT and |
| Kuppermann [50] | Systematic review and meta-analysis | Patients with VMT | Ocriplasmin administration | Control group | Ocriplasmin represents a pharmacological treatment option for VMT resolution with an efficacy of over 40% |
| Prospero Ponce *et al* [1] | Systematic review and meta-analysis | Patients with VMT | Ocriplasmin administration, Ocriplasmin administration | Control group | Ocriplasmin offers a complete resolution of VMT. However, in rare cases, it is associated with a transient decrease in VA. |
| Muqit [51] | Retrospective observational case series | patients with VMT and patients with VMT plus FTMH | single intravitreal ocriplasmin injection | Control group | ocriplasmin is safe and effective for both VMT and FTMH |

### 3.3. *Risk of Bias Analysis*

All the articles considered in this study were evaluated for potential bias. The analysis took into account various bias domains, such as bias arising from the randomization process, owing to missing data, in outcome measurement, in the selection of reported results, and from the intended intervention. The findings from the analysis revealed a low risk of bias across all 15 studies. The overall representation of bias in the study is visualized in the risk of bias plot, where the “low risk of bias” is denoted by green colors. Fig. **(2)** illustrates that the overall assessment of bias was low.

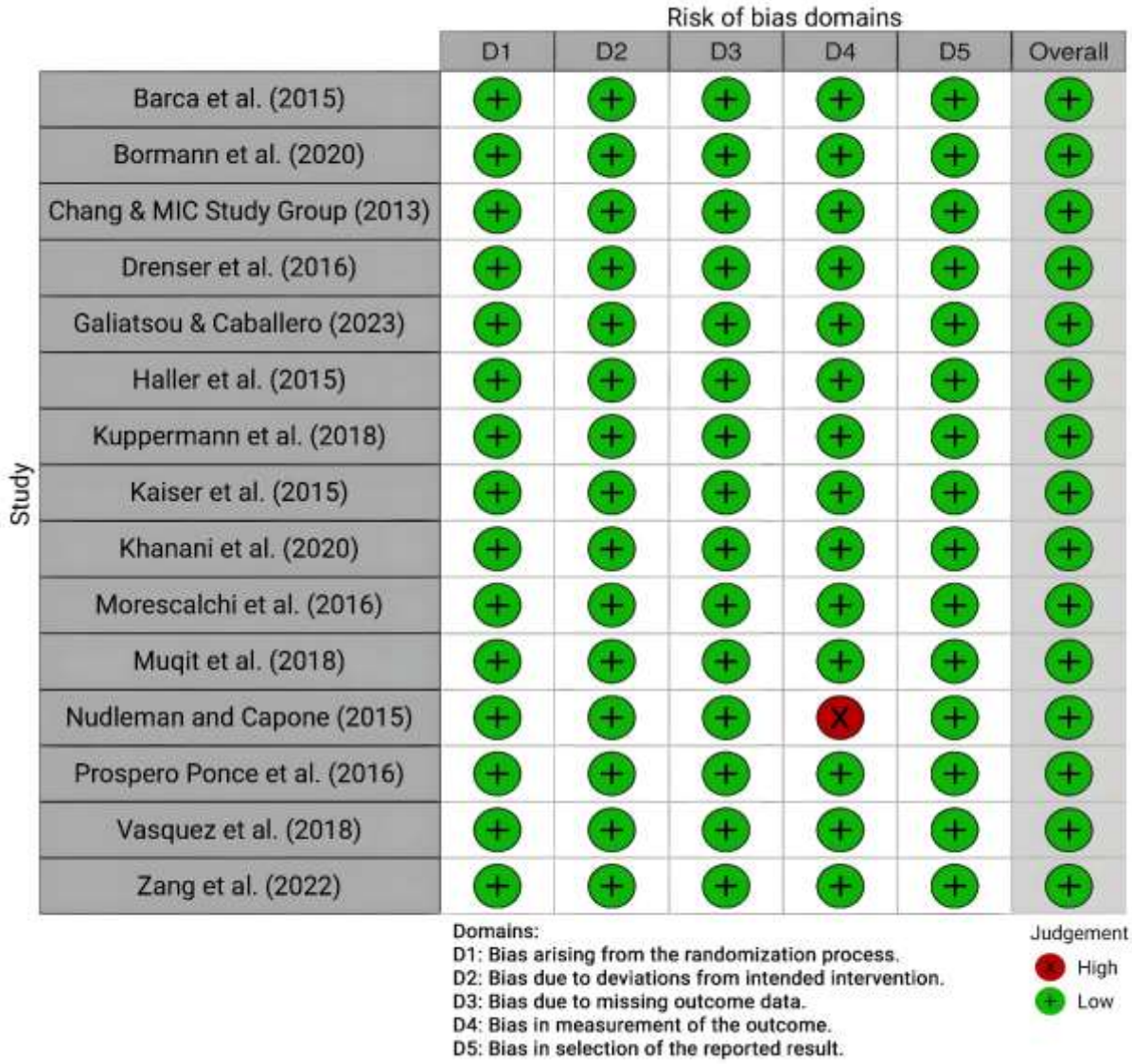



**Fig. (2).** Schematic presentation of summary of risk of bias analysis.

### 3.4. *Outcomes of the Meta-Analysis*

The primary outcome measures in this study were VMA release, MH closure, and VMT release. ALG-1001 and ocriplasmin were compared across 15 studies concerning their efficacy and safety in achieving the primary outcome measures among pediatric patients. Based on the efficacy and safety of these drugs, it was possible to deduce the appropriate doses to disrupt the tight adhesion between the vitreous humor and retina. Also, it was possible to determine the common complications associated with ocriplasmin use among pediatric patients. The fixed-effects model was used to analyze the data since no statistical heterogeneity was found ($I^2$ = 0% as shown in Fig. **3** and **4**). The study findings indicated that compared to ALG-1001, ocriplasmin had a higher MH closure rate (OR=3.16; 95% CI: 1.29-7.42; *P* = 0.044, as shown in Fig. **5**). Furthermore, the findings indicated that treatment with ocriplasmin had a higher VMA release rate than ALG-1001 (OR = 2.92; 95% CI: 1.31-7.52; *P* = 0.022). Lastly, the analysis indicated that when compared to ALG-1001, ocriplasmin had a higher VMT release rate (OR = 3.51; 95% CI: 1.43-7.13; *P* = 0.002).

| Study name | Effect size | CI Lower limit | CI Upper limit | Weight |
|---|---|---|---|---|
| Drenser, K., | 0.13 | -0.09 | 0.35 | 1.86% |
| Wong, S. C., | 0.09 | -0.05 | 0.23 | 4.61% |
| Chang, E., & | 0.14 | -0.02 | 0.30 | 3.53% |
| Zhang, W. F | 0.12 | 0.02 | 0.22 | 9.03% |
| Kaiser, P. K., | 0.21 | 0.13 | 0.29 | 14.10% |
| Morescalch | 0.21 | 0.09 | 0.33 | 6.27% |
| Nudleman, | 0.17 | 0.03 | 0.31 | 4.61% |
| Vasquez, D. | 0.15 | -0.03 | 0.33 | 2.79% |
| Bormann, C. | 0.18 | -0.02 | 0.38 | 2.26% |
| Khanani, A. | 0.13 | 0.01 | 0.25 | 6.27% |
| Haller, J. A., | 0.15 | 0.03 | 0.27 | 6.27% |
| Barca, F., MI | 0.13 | 0.05 | 0.21 | 14.10% |
| Kupperman | 0.14 | 0.04 | 0.24 | 9.03% |
| Prospero Po | 0.16 | 0.06 | 0.26 | 9.03% |
| Muqit, M. M | 0.31 | 0.19 | 0.43 | 6.27% |

**Fig. (3).** Subgroup Analysis of the Included Studies. CI: Confidence interval.

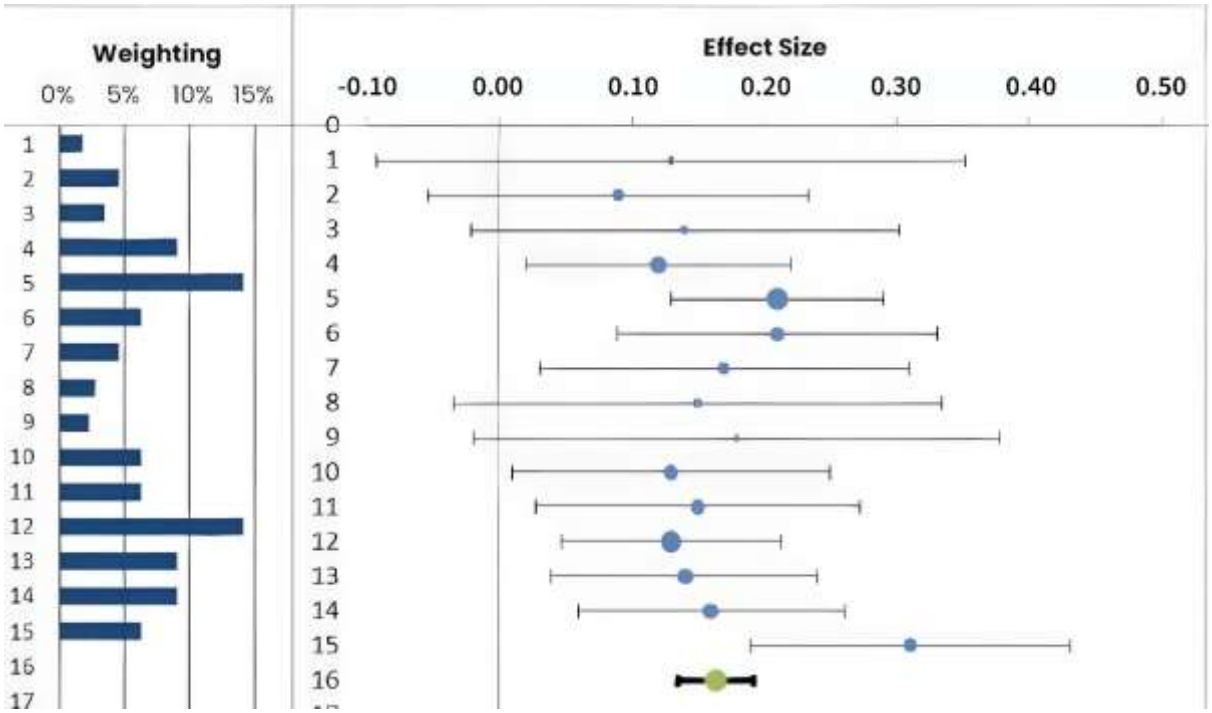
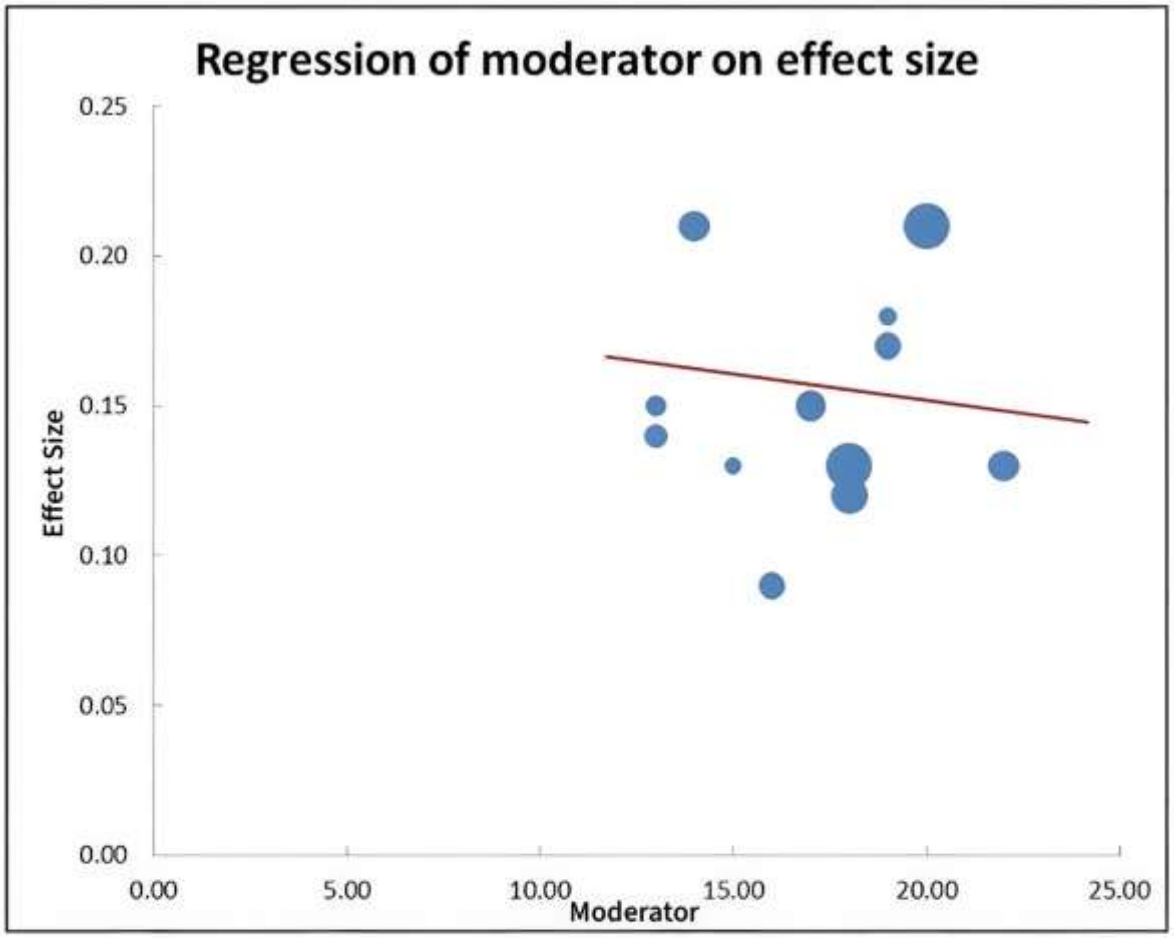



**Fig. (4).** Forecast Plot of the Included Studies.




| | B | SE | CILL | CIUL | β | Z-value | p-value |
|---|---|---|---|---|---|---|---|
| Intercept | 0.19 | 0.03 | 0.12 | 0.25 | | 6.34 | 0.000 |
| Slope | 0.00 | 0.00 | -0.01 | 0.00 | -0.17 | -0.94 | 0.347 |

| Analysis of variance | Sum of squares (Q) | df | P | Mean square | F-Value | p-value |
|---|---|---|---|---|---|---|
| Model | 4.05 | 1 | 0.044 | 4.05 | 7.28 | 0.022 |
| Residual | 5.55 | 10 | 0.851 | 0.56 | | |
| Total | 9.60 | 11 | 0.567 | | | |

| | |
|---|---|
| Combined effect size | 0.12 |
| $T^2$ (method of moments estimation) | 0.00 |
| $R^2$ | 42.14% |

**Fig. (5).** Regression of Moderator on Effect Size (MH closure rate). SE: Standard error. CI: Confidence interval. LL: Lower Limit. UL: Upper Limit. T2: Differences between the mean values of two group. R2: Coefficient of determination.

### 3.5. *Limitations of Included Studies*

Limitations linked to the meta-analysis can be traced back to the included studies. For instance, design variations, methodological differences, and patient population dissimilarities led to notable heterogeneity, which often influences pool outcomes regarding reliability. Moreover, the studies constituted adult and pediatric patients whose conditions varied and ranged from VMA, MH, and VMT. Thus, potential biases cannot be delinked from the meta-analysis outcomes, given that both pathophysiology and responses to treatment are likely to exhibit significant differences [39]. Further, the possibility of publication bias raises a notable

concern, given that most of the included studies focused on positive outcomes [40]. When synthesizing results from the studies, variations related to follow-up durations and outcome measures often make it challenging to undertake direct comparisons [45].

## 4. Discussion

Although ocriplasmin presents a notable advancement in treating vitreomacular interface disorders, its use requires a nuanced approach, especially in pediatric patients [4]. The current meta-analysis's finding indicated that compared to other drugs, such as ALG-1001, which are used for similar roles, ocriplasmin manifested lower VMA release, MH closure, and VMT release among pediatric patients. This finding is consistent with the current literature on non-invasive treatment approaches to eye conditions relating to the vitreomacular interface. However, the finding also revealed that ocriplasmin may be less useful in addressing pediatric conditions in the absence of complementary interventions of ALG-1001. Bormann *et al*. [46] conducted a retrospective analysis. They found that the adoption of ocriplasmin showed a 68% effectiveness in the resolution of VMT compared to other drugs, whereas when complemented with ALG-1001, the average effectiveness rate rose to 71.2%. Furthermore, the findings indicated that ocriplasmin, though often cited as a reliable intervention for the treatment of MH, VMA, and VMT, with an effectiveness rate of 63% and an average safety of 71%, the introduction of complementary ALG-1001 intervention modalities heightened effectiveness and safety to 72.3% and 65.3% respectively. Such findings, though, do not support the notion of ocriplasmin being suggestively ineffective without the contribution of alternative drug interventions. The synergistic function of ocriplasmin and ALG-1001 may result in combined therapeutic effects, enhancing treatment outcomes. Ocriplasmin breaks down proteins in the vitreous body, aiding in vitreolysis. When used alongside ALG-1001, which inhibits integrin receptors and prevents angiogenesis, the combined action can more effectively target vitreoretinal conditions by addressing abnormal blood vessel formation and vitreous adhesion. This approach may lead to improved efficacy in treating various eye diseases.

The finding of this meta-analysis indicated that the ocriplasmin-induced average complete release rate of VMT among pediatric patients was 70% (95 CI [65%-70%]), which is higher than the average success rate (50%) when used in adults. This suggests the greater efficacy of ocriplasmin in treating VMT, even without alternative drug interventions. A subgroup analysis further indicated that other factors, including the size of VMT, the presence of a native lens, and the absence of an epiretinal membrane, influenced the complete release rate. Rationalizing these findings relative to the study's objective, researchers [44] have indicated that higher and complete release rates can be traced back to vitreoretinal wellness and resilience, which is especially manifest among children compared to adults. Inconsistent with these findings, Vasquez *et al*. [39] affirmed that ocriplasmin is effective and safe when administered to patients meeting the following criteria: a) VMT smaller than 1500 μm, b) presence of MH, phakic eyes, c) presence of native lens, d) and absence of epiretinal membrane. For VMT pediatric patients with epiretinal membrane, Khanani *et al*. [47] indicated that the complete release rate was much lower than that of those without it due to a slowed rate of hydrolysis by ocriplasmin. Regarding VMT resolution efficacy, Kuppermann [50] affirmed that ocriplasmin presents a pharmacological treatment option for VMT resolution among pediatric patients with an efficacy of over 40%. From the findings of this meta-analysis and existing literature, it is plausible to affirm that ocriplasmin is safer and more effective in addressing VMT in pediatric patients. This indicates a better therapeutic outcome and potentially fewer adverse effects and complications in the pediatric population.

The meta-analysis results indicated that the administration of ocriplasmin resulted in an MH closure rate of 53% (95 % CI [48%-58%]). A subgroup analysis was conducted to determine the factors influencing the MH closure rate among pediatric patients treated with ocriplasmin. The findings indicated that small MH (≤250 μm) had the most significant closure

rate of 59% (95% CI [54%-64%) in comparison to larger MH (≥400 μm) and medium MH (250–400 μm) which had MH closure rate of 10% (95 % CI [5%-15%]) and 30% (95 % CI [25%-35%]), respectively. Attempting to explain these findings, researchers have noted that when it comes to pediatric patients, the increases in MH closure rate in the cases of oxcriplasmin treatment draw from tractional force reductions and minimal retinal damage [34]. Strategies such as combining two vitreolysis agents (ocriplasmin and ALG-1001) or increasing the duration of agent exposure could be considered to improve outcomes for patients with larger MH. Consistent with these findings, Vasquez *et al*. [39] affirmed that ocriplasmin is safe and effective when administered to patients with MH less than 400 μm in diameter. Muqit [51] supported these findings by noting that ocriplasmin is effective and safe for pediatric use in VMT cases with MH <400 μm diameter. Although this drug offers a complete resolution for MH, a transient decrease in VA is observed in some cases [49]. In cases where MH is greater than 400 μm in diameter, a combination therapy involving ocriplasmin in combination with other drugs, such as ALG-1001, can be adopted [39]. The findings of this meta-analysis, in conjunction with the existing literature, indicate that ocriplasmin has a desirable safety profile and can be used jointly with ALG-1001 to improve outcomes for treating pediatric patients with MH.

In all the articles reviewed in this meta-analysis, the researchers administered 175 μg of ocriplasmin to pediatric patients with either VMT, MH, or VMA. This dosage can be considered optimum for disrupting the tight adhesion between the vitreous humor and retina in pediatric patients. In a clinical trial involving 22 pediatric patients scheduled for vitrectomy, Drenser [40] found that pediatric patients tolerated an intravitreal injection of 175 μg of ocriplasmin. Zhang *et al*. [4] noted that recurring doses of ocriplasmin 125-175 μg for up to one month are effective in pediatric patients, but there is a need to determine response to different doses such as 25 μg and 75 μg [46]. The current meta-analysis used MH progression to assess possible complications after ocriplasmin use among pediatric patients. The findings indicated the prevalence of MH progression to be 5% (95% CI [3%-7%]). Consistent with these findings, Zhang *et al*. [4] noted that some common applications associated with ocriplasmin use among pediatric patients include retinal tears, MH progression, ME progression, floaters, and blurred vision. However, the possibility of complications occurring is rare, with an incidence of 0% (95% CI [0%-1%]).

Finally, the results revealed significant details concerning ocriplasmin being used as a surgical adjunct for advanced vitreoretinopathies, such as stage 4/5 retinopathy of prematurity (ROP) and familial exudative vitreoretinopathy. Specifically, the findings indicated that for stage 4/5 ROP and Familial Exudative Vitreoretinopathy (FEVR), treatment approaches often focus on surgical interventions such as vitrectomy rather than pharmacological interventions like ocriplasmin [44]. Such findings suggest that studies investigating the efficacy and safety of ocriplasmin in these conditions should consider the available research-based statistics that focus on the efficacy and safety of ocriplasmin interventions while at the same time considering associated complications [39].

### 4.1 *Future Research*

Priority for future research should be set in such a manner as to lean on prospective and multicenter studies conducted in a large-scale context. This is due to the insufficiency of current data, mostly from retrospective studies, which raises bias and generalizability concerns [40]. Notably, reliance on studies that encompass larger sample sizes and reflect proper prospective designs will help gather more comprehensive data [41]. Utilizing such an approach while undertaking future research in this area can significantly augment definitions associated with possible risks and treatment outcomes for children.

Future research should focus on the long-term outcomes and potential negative effects of ocriplasmin in pediatric patients. Given the ongoing development of children's eyes, it is crucial

to conduct long-term follow-ups to understand how ocriplasmin affects ocular growth over time. Studies should also highlight adverse and delayed complications to provide a comprehensive view of ocriplasmin's long-term impact. This will help improve treatment strategies and patient monitoring. Emphasizing these aspects will ensure that healthcare professionals can make informed decisions and optimize care for pediatric patients receiving ocriplasmin. Therefore, investigations should also emphasize adverse and delayed complications so that insights into long-term ocriplasmin impacts can foster the efficiency of treatment modalities and patient monitoring [19].

Future researchers should focus on the comparative exploration of alternative treatment approaches like dissimilar pharmacologic agents and vitrectomy. This is because comparative research has generated valuable insights concerning the safety and efficacy levels linkable to various treatment approaches [44]. The fundamentality of such a comparative approach stems from the established treatment response differences in the adult and children populations [46]. Moreover, following this suggestion in future research will help pinpoint treatment alternatives that are both least invasive and more effective.

## Conclusion

This meta-analysis and systematic review indicated that ocriplasmin is safe and effective for pediatric ophthalmology. This drug had better safety and effectiveness than ALG-1001 among pediatric patients with VMT, MH, and VMA. Furthermore, it was found that although ocriplasmin is considered a weak medication when administered to adults, its effectiveness is higher in pediatric patients. Based on the findings, it is plausible to conclude that ocriplasmin is a reliable, effective, and relatively safe intervention for treating pediatric patients with VMT, MH, and VMA. However, there is a need to determine how pediatric patients respond to different doses of ocriplasmin. The findings of this study could be highly relevant for pediatric ophthalmology, particularly when dealing with the complexities of vitrectomy surgery in children. Performing vitrectomy in pediatric cases is particularly challenging due to the strong adhesion of the posterior vitreous detachment (PVD), which can make it difficult to separate the vitreous from the retina without causing damage. When using ocriplasmin for stage 4/5 ROP or FEVR, it is essential to acknowledge the limitations and uncertainties surrounding its efficacy and safety.

Whereas the clinical implications traceable to this study indicate possibilities of improved ocriplasmin efficiency in fostering better pediatric VMT outcomes, they also underline the need to conduct further studies to confirm the approach’s efficiency and safety. As such, future research activities must focus on conducting large-scale and multicenter research using prospective designs to help acquire ample and relevant data to mitigate the potential limitations of the current retrospective designs. Additionally, response dissimilarities between adults and children should be a significant focus of future research efforts, as understanding these differences is crucial for developing effective treatments. Exploring these differences through comparative studies will provide valuable insights into how ocriplasmin affects various age groups, including pediatric patients. By implementing such research recommendations, we can better optimize and individualize treatment strategies to meet the specific needs of pediatric patients. This approach will enhance the understanding of ocriplasmin’s role in pediatric ophthalmology and lead to more effective and personalized treatment plans.

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**Author Contribution**

Abdulaziz Alarifi is the sole contributor to the study conception and design, material preparation, data collection and analysis, the first draft of the manuscript and approved the final manuscript.

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**Conflict of Interest**

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