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OPEN PEER REVIEW

The Impact of Oral Sildenafil on Retinopathy of Prematurity in Very Preterm Newborns with Early-Onset Pulmonary Hypertension: A Retrospective Cohort Study

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

3 comments · 7 Nov 2025 – 18 Nov 2025

Referee 1 Reviewer

MAJOR REVISION 7 Nov 2025

Comments:
1. Report RR instead of OR in the abstract and body.
2. Estimate the sample size based on the main aim.
3. P = 1 is not correct. Report it as >0.99.
4. Wide confidence intervals, such as 0.98–50.92, are not acceptable.

Associate Editor

MAJOR REVISION 15 Nov 2025

Title: The Impact of Oral Sildenafil on Retinopathy of Prematurity in Very Preterm Newborns with Early-Onset Pulmonary Hypertension: A Retrospective Cohort Study
The topic is clinically relevant and addresses an important safety concern regarding the off-label use of sildenafil in preterm infants with pulmonary hypertension. The study is timely and could add valuable data to the limited literature on this subject.

Comments:
- The classification of ROP should follow the internationally accepted distinction between Type 1 (treatment-requiring) and non–treatment-requiring ROP, which integrates both stage and "plus" disease. Focusing solely on ROP stage (e.g., stage ≥3) without accounting for "plus" disease may misclassify cases and obscure clinically significant findings. The authors should clarify how "plus" disease was incorporated into outcome assessment and ideally reanalyze the data based on treatment requirement or Type 1/Type 2 classification.
- The control group appears heterogeneous, with unclear information on what pharmacologic management (if any) was provided for pulmonary hypertension. Since institutional protocols differ, the authors should specify which alternative drugs were used in the unexposed group and discuss whether differences in NICU practice (between Shariati and Imam Khomeini hospitals) could have introduced bias.
- The sample size (n = 74) is small for a retrospective study with multiple covariates. The authors are encouraged to report the post hoc statistical power to detect a clinically meaningful difference in severe ROP incidence between groups. If the power is below 80%, the risk of Type II error should be explicitly acknowledged. Any power < 0.8 would make the study underpowered and its conclusions exploratory rather than confirmatory.
- The discussion appropriately references prior literature but should be more cautious in interpreting the lack of association as evidence of safety, given the study's limited power and potential confounding from different hospital protocols. Statements about "ocular safety" should be tempered to "no significant association was observed," pending larger prospective trials.

Editor-in-Chief

MAJOR REVISION 18 Nov 2025

Dear Author,
We have reviewed your manuscript carefully. This is to inform you that this manuscript needs major revision.
Kind Regards
EIC

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Reviewer:

We thank the reviewer for their thoughtful and constructive feedback. All comments have been carefully addressed, and the manuscript has been revised accordingly. For the reviewers' convenience, all changes have been highlighted in yellow in the revised text.

Reviewers' Comments:

Reviewer 0:
Comments:
1. Report RR instead of OR in the abstract and body.

Response:

We thank the reviewer for this comment. Although the study was designed as a retrospective cohort, our primary analytic approach was fundamentally a case control comparison of exposed (sildenafil treated) versus unexposed (sildenafil untreated) infants with respect to the odds of developing severe ROP. In this context, the odds ratio is an appropriate and widely accepted measure of association, particularly because severe ROP (stage ≥3) was relatively uncommon, meaning that the odds ratio closely approximates the relative risk. Logistic regression provided stable and interpretable estimates, whereas models designed to yield relative risks did not converge reliably due to the rarity of the outcome and the covariate structure.

2. Estimate the sample size based on the main aim.

Response:

We appreciate the reviewer's comment regarding sample size estimation. Because this investigation was a retrospective cohort based on all available premature infants with early onset pulmonary hypertension, a prospective sample size calculation was not feasible. The use of oral sildenafil for the study population in our setting is protocol dependent, resulting in a naturally limited number of exposed infants. Moreover, the outcome of interest, severe ROP, is relatively rare, and its true prevalence within this highly specific clinical subgroup was not known beforehand, making conventional sample size planning unreliable. For these reasons, we included all eligible cases during the study period, which is the standard approach for retrospective studies constrained by the underlying number of treated infants and the rarity of both the exposure and the outcome. In this revision, we have clarified this limitation in the manuscript to justify why a formal a priori sample size calculation was not performed, as provided below:

"Because the use of oral sildenafil in the study setting was protocol dependent and severe ROP was a rare outcome, a formal a priori sample size calculation was not feasible, and the study relied on all available eligible infants during the study period."

3. P=1 is not true. Report as >0.99

Response:

Thank you for the comment. We have corrected all instances of P = 1 and now report them as P > 0.99 as recommended.

4. The wide confidence intervals such as: 0.98-50.92 are not acceptable.

Response:

Thank you for this comment. In this revision, we carefully reexamined the covariates included in our regression models to enhance model stability and reduce excessively wide confidence intervals. We also focused the reporting of findings on the odds ratios describing the association between sildenafil treatment and severe ROP, which were not statistically significant both in the unadjusted analysis (OR: 0.84, 95% CI: 0.30-2.34, P = 0.7) and after adjustment for relevant clinical covariates (adjusted OR: 0.70; 95% CI: 0.17-2.77, P = 0.6). The updated models now yield more stable and interpretable estimates.

Associate Editor's Comments:

Reviewer Comment 1

Comment:
The classification of ROP should follow the internationally accepted distinction between Type 1 (treatment-requiring) and non–treatment-requiring ROP, which integrates both stage and “plus” disease. Focusing solely on ROP stage (e.g., stage ≥3) without accounting for “plus” disease may misclassify cases.

We thank the reviewer for this important suggestion. We revised the ROP screening and classification subsection of the Methods to explicitly state that ROP was classified according to the International Classification of Retinopathy of Prematurity (ICROP), incorporating disease stage, retinal zone, and the presence of plus disease. We clarified that treatment-requiring ROP (Type 1 ROP), as determined by a pediatric retina specialist according to international treatment criteria, was used as the primary clinically relevant outcome, while stage-based severity was reported descriptively. The Results section and Table 3 were revised accordingly to emphasize treatment-requiring ROP.

Reviewer Comment 2

Comment:
The control group appears heterogeneous, with unclear information on what pharmacologic management was provided for pulmonary hypertension. The authors should specify which alternative drugs were used and discuss whether differences in NICU practice could have introduced bias.

We have clarified the management of pulmonary hypertension in both study groups in the Study Design and Population section of the Methods. We now specify that neither hospital had access to inhaled nitric oxide during the study period. Standard care in both NICUs included conservative management, such as sedation, ventilation optimization, maintenance of oxygen saturation at 92–95%, and inotropic support with milrinone or dobutamine when indicated. We also clarified that oral sildenafil was added to routine care only at Shariati Hospital and was not used at Imam Khomeini Hospital. In the Discussion, we explicitly acknowledge that this hospital-based allocation may introduce residual confounding related to institutional differences in care practices.

Reviewer Comment 3

Comment:
The sample size is small for a retrospective study with multiple covariates. The authors are encouraged to report post hoc power and acknowledge the risk of Type II error.

We agree with the reviewer and addressed this concern by adding a statement at the end of the Statistical Analysis section noting that, given the limited sample size, the study was primarily powered to detect large differences between groups. In the Discussion (Limitations), we explicitly acknowledge that the study may be underpowered to detect small or moderate effects, that the possibility of Type II error cannot be excluded, and that the findings should therefore be interpreted as exploratory rather than confirmatory.

Reviewer Comment 4

Comment:
The discussion should be more cautious in interpreting the lack of association as evidence of safety, given the study's limited power and potential confounding.

We revised the Discussion and Conclusion to remove language implying ocular safety. Statements suggesting safety were replaced with more cautious language indicating that no statistically significant association was observed between sildenafil exposure and ROP outcomes in this cohort. We also emphasized the study's limited statistical power and potential institutional confounding and highlighted the need for larger prospective studies before definitive conclusions can be drawn.

2 Revision 1

2 comments · 29 Dec 2025 – 28 Feb 2026

Referee 1 Reviewer

MAJOR REVISION 29 Dec 2025

Comments:
1. Report RR instead of OR in the abstract and body.
2. Revise “P-value > 0.9”.
3. Referring to case and control groups in cohort studies doesn’t make sense.
4. Estimate the sample size based on the main aim.
5. Wide confidence intervals such as 1.00-14.5 are not acceptable.

Editor-in-Chief

MAJOR REVISION 28 Feb 2026

Major Revision

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editors and Reviewers,

We thank the reviewers for their thoughtful and constructive feedback. All comments have been carefully addressed, and the manuscript has been revised accordingly. For the reviewers' convenience, all changes have been highlighted in yellow in the revised text.

Reviewers' Comments:

1. Report RR instead of OR in the abstract and body.

Response: Thanks indeed for this insightful comment based on the cohort study design. In this revision, we did revise the statistical analysis methodology and results to use Poisson regression in order to calculate crude and adjusted relative risk (RR) for the evaluation of the association between sildenafil exposure and ROP incidence.

2. Revise "P-value > 0.9".

Response: Thank you for this comment. We have corrected all instances of P-value reporting as recommended.

3. Talking about the case and control groups in the cohort studies doesn't make sense.

Response: With thanks for this comment, we agree with the reviewer on this query. In this regard, we have revised all instances of case and control wording in this revision to sildenafil exposed and unexposed to fully comply with the cohort study design.

4. Estimate the sample size based on the main aim.

Response: We sincerely thank the reviewer for this comment. This was a retrospective cohort study utilizing a convenience sample of eligible cases from two tertiary NICUs during the specified study period (2017–2022). Rather than employing a prospective power calculation, we conducted a post-hoc sample size assessment based on the available cohort. Of 303 consecutive neonates screened with early-onset pulmonary hypertension, 74 met the inclusion criteria (gestational age ≤31 weeks, complete follow-up data, ROP screening performed according to guidelines). The final sample comprised 38 sildenafil-exposed and 36 unexposed infants.

Post-hoc power analysis indicated that with this sample size and observed outcome rates (68.6% ROP in exposed, 72.2% in unexposed), the study could detect a risk ratio of approximately 0.50 (50% risk reduction) with 80% power at $\alpha = 0.05$. While the study was underpowered to detect the small observed effect (RR = 0.95), it was adequately powered to exclude clinically important protective effects (RR ≤ 0.50) or harmful effects (RR ≥ 1.5) of sildenafil on ROP development.

We added the details to methods section and acknowledged the sample size issue in the limitations.

5. The wide confidence intervals such as: 1.00-14.5 are not acceptable.

Response: Thanks for this wise observation. As we have changed the regression method to calculate RR in this revision, such wide confidence intervals were no more observed in results. Besides, to comply with robust use and interpretation of the regression analysis, we have revised the criteria to include the covariates in the adjusted model, and in result none of the covariates were independently significant in the adjusted model. Therefore, we decided to remove Table 4 and report the results of models in text of results only.

3 Revision 2

2 comments · 4 Jun 2026 – 6 Jun 2026

Associate Editor

MINOR REVISION 4 Jun 2026

Comments:
1. Revise “P-value > 0.9”.
2. Where is Table 4?
3. The wide confidence intervals, such as 1.00-14.5, are not acceptable.

Editor-in-Chief

MINOR REVISION 6 Jun 2026

Dear Author,
We have reviewed your manuscript carefully. This manuscript needs minor revision in response to the reviewers' comments.
Kind Regards
EIC

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Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Reviewer,

We sincerely thank you for your careful review and valuable comments. We have addressed your concerns as follows:

Comment 1: Revise “P-value > 0.9”.

Response: Thank you for this comment. In the first round of revision, values rounded to 1 were initially reported as "P = 1". However, following a reviewer’s recommendation, we revised the formatting and replaced these values with "P > 0.9". Therefore, the current presentation of these P values in the revised manuscript reflects the recommendation provided during the previous round of review. We have also carefully rechecked the manuscript to ensure consistency throughout.

Comment 2: Where is Table 4?

Response: Thank you for this comment. In the current revision, the regression model was modified and the previous Table 4 was removed accordingly. The revised regression results are now presented in the Results section of the manuscript, and therefore, Table 4 is no longer included.

Comment 3: The wide confidence intervals, such as 1.00–14.5, are not acceptable.

Response: Thank you for this important comment. In the current revision, the regression model was revised, and the previous Table 4, which contained the estimate with a wide confidence interval, was removed. Consequently, the estimate referred to by the Associate Editor is no longer present in the revised manuscript. In addition, we carefully reviewed the Discussion section and removed residual statements related to the previous model to ensure consistency between the Results and Discussion. We agree that estimates with wide confidence intervals should be interpreted cautiously, and the revised manuscript emphasizes the exploratory nature of our findings and the need for larger prospective studies.

4 Revision 3

2 comments · 21 Jun 2026 – 21 Jun 2026

Associate Editor

MINOR REVISION 21 Jun 2026

Comments:
1. Revise “P-value > 0.9” to “P>0.99”.
2. Report the results of multivariable Poisson regression in a table.

Editor-in-Chief

MINOR REVISION 21 Jun 2026

Dear Author,
We have reviewed your manuscript carefully. This manuscript needs minor revision based on the reviewers' comments.
Kind Regards
EIC

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Revision 4

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Reviewers,

1. Thank you very much for your valuable and constructive comments. All changes made in the revised manuscript have been highlighted in yellow for ease of review.

We revised the reported P values, changing values reported as >0.9 to >0.99 where appropriate.

2. We have added a table reporting the results of the multivariable Poisson regression analysis.

5 Revision 4

2 comments · 4 Jul 2026 – 8 Jul 2026

Associate Editor

ACCEPT 4 Jul 2026

Accept

Editor-in-Chief

ACCEPT 8 Jul 2026

Dear Authors,
This is to inform you that your manuscript has been accepted for publication.
Kind Regards
EIC