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REVIEW

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Serum 25-hydroxyvitamin D levels in infants with retinopathy of prematurity: a systematic review and meta-analysis

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Abstract

Purpose To evaluate the association between serum vitamin D levels and retinopathy of prematurity (ROP) through a systematic review and meta-analysis.

Methods A systematic search was conducted in PubMed, Embase, The Cochrane Library, Web of Science, and Scopus up to August 2026. All observational studies measuring vitamin D levels in infants with ROP were included. The standardized mean difference (SMD) was calculated using a random-effects model to assess differences in vitamin D levels between patients with ROP and healthy controls. The log odds ratio (OR) was computed to assess the association between vitamin D deficiency and the incidence of ROP.

Results Ten relevant studies evaluating the relationship between vitamin D and ROP were included. Six studies, including 281 ROP infants, compared serum vitamin D levels between ROP and control groups. Five studies compared the risk of ROP development in the vitamin D-sufficient vs. deficient infants. Meta-analysis results revealed a significantly lower vitamin D level in ROP infants vs. control (SMD: -0.94, 95% CI: -1.21 to -0.67; $I^2 = 48.26\%$, p-value < 0.001). Additionally, vitamin D levels were significantly lower in infants requiring ROP treatment than in the monitoring group. Furthermore, infants with vitamin D deficiency had a higher risk of ROP development (OR: 6.69, 95% CI: 1.65 to 27.4, $p = 0.01$).

Conclusion The findings of the current study suggest that vitamin D status may be associated with the risk and severity of ROP in preterm infants. Further well-designed prospective studies are needed to determine whether vitamin D status has an independent role in ROP and whether supplementation provides clinical benefit.

Keywords Retinopathy of prematurity, Vitamin D, 25-hydroxyvitamin D, ROP, Meta-analysis

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Introduction

Retinopathy of prematurity (ROP) is a vaso-proliferative retinal disorder occurring in preterm infants and represents one of the leading causes of childhood blindness [1, 2]. The prevalence of ROP is estimated at 31.9%, while the prevalence of severe ROP is 7.5% [3].

ROP progresses with the cessation of retinal vascular development in premature infants due to high oxygen levels, followed by hypoxia-induced pathological neovascularization at birth [1]. Among the angiogenesis-related factors, vascular endothelial growth factor (VEGF) and angiogenin hold critical importance [4].

Vitamin D is a micronutrient involved in modulating inflammation, angiogenesis, oxidative stress, and fibrosis [4]. In addition, it contributes to cellular growth and differentiation. The presence of vitamin D receptors in ocular cells suggests a localized regulatory function [5]. The role of vitamin D in retinopathy encompasses multiple aspects. It provides antioxidant protection by preserving mitochondrial function and neutralizing free radicals, thereby reducing oxidative stress-induced damage to the retina and optic nerve. Additionally, vitamin D influences immune regulation by modulating T cell subsets and inhibiting pro-inflammatory signaling pathways. Furthermore, vitamin D influences the pathophysiology of ROP by regulating VEGF expression through oxygen-dependent mechanisms [4, 5].

Premature infants, especially those who are born before 32 weeks of gestation, are at heightened risk of vitamin D deficiency due to incomplete transplacental transfer occurring in the third trimester [5]. Recent studies have reported lower serum 25-hydroxyvitamin D levels in preterm infants who developed ROP compared to healthy infants [5–7]. Moreover, a stage-specific association between vitamin D and VEGF levels in preterm infants has been observed, suggesting the role of vitamin D across different phases of ROP [4]. Given the limited scientific evidence and ongoing uncertainties regarding the role of vitamin D in the pathogenesis and progression of ROP, as well as the lack of standardized protocols for prevention, diagnosis, and treatment, there is a critical need for a systematic review on this topic. The present study aims to systematically assess serum vitamin D levels in patients with ROP.

Materials and methods

This systematic review and meta-analysis were conducted in accordance with the PRISMA guideline and prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration code: CRD420251052527. The study protocol was also approved by the Institutional Review Board of Isfahan University of Medical Sciences (approval code: IR.ARI.MUI.REC.1404.133). Before commencement, all authors reviewed and agreed upon the predefined inclusion and exclusion criteria.

Search strategy

A systematic search was performed using the PubMed, Scopus, Embase, The Cochrane Library, and Web of Science databases for relevant articles published up to August 2026. To avoid missing any relevant studies, the reference lists of all included studies were manually screened. Additionally, the first 200 articles in Google Scholar were screened. The search utilized MeSH terms and keywords including: "Retinopathy of Prematurity" OR "Prematurity Retinopathies" AND "25-Hydroxyvitamin D" OR "Vitamin D" OR "calcidiol" OR "calcifediol" OR "25OHD". No restrictions were placed on publication date or language. The detailed search strategy for each database is provided in Supplementary Table 1.

Inclusion and exclusion criteria

Two reviewers (E.F. and M.P.) independently screened studies for eligibility. Any disagreements were resolved through consultation with a third reviewer (M.M.). Studies were included if they met the following criteria: [1] original human research; [2] investigated the association between ROP and vitamin D levels; [3] employed a standard method for measuring serum vitamin D concentrations; and [4] enrolled patients with a confirmed diagnosis of ROP. Exclusion criteria encompassed: review articles, letters, editorials, case reports, case series, book chapters, in vitro studies, and duplicate publications. There were no geographical, racial, or ethnic restrictions. Studies that included participants with comorbid conditions or the use of medications known to influence vitamin D status were also excluded.

Data extraction

Following the removal of duplicate records using EndNote software (version 21), two authors (E.F. and A.D.) independently assessed the titles and abstracts, and subsequently the full texts, of the remaining studies against the eligibility criteria. Data were extracted independently using a standardized data extraction form in Microsoft Excel (Microsoft, Redmond, WA, USA), following Cochrane guidelines. Discrepancies were resolved by adjudication from the third reviewer (M.P.).

The extracted data included: [1] study characteristics (first author, publication year, country of origin, geographic coordinates); [2] participant demographics (sample size, sex, gestational age, birth weight); [3] vitamin D assessment details (timing of measurement, assay method, mean serum levels, prevalence of deficiency based on study-defined cut-offs); and [4] ROP-related outcomes (screening schedule and treatment

requirement). The extracted data were verified for accuracy by a third author (M.P.).

Quality assessment

The methodological quality of the included studies was evaluated independently by two reviewers (E.F. and A.D.) using the Joanna Briggs Institute (JBI) critical appraisal checklist for case-control and cross-sectional studies [8].

Statistical analysis

All statistical analyses were performed using Stata software, version 17 (StataCorp LP, College Station, TX, USA). The pooled Standardized Mean Difference (SMD) was calculated to compare the mean vitamin D levels between ROP and control groups, and between treatment-requiring and non-treatment-requiring ROP groups. The restricted maximum likelihood (REML) model was applied. The log odds ratio (OR) was computed to assess the association between vitamin D deficiency and the incidence of ROP. The results were then back-transformed to the odds ratio (OR) scale by applying the exponential function (OR = exp (Log OR)) for easier clinical interpretation and reporting.

Heterogeneity was quantified using the I^2 statistic and Cochran's Q test. A p-value < 0.05 for the Q-test was considered statistically significant. Subgroup analyses were performed based on the timing of vitamin D assessment to explore potential sources of heterogeneity. A leave-one-out sensitivity analysis was conducted to evaluate the individualized effect of each study on the meta-analysis results. Publication bias was assessed both visually using funnel plots and statistically using Egger's test.

Results

Literature search and study selection

A total of 1020 articles were identified through the systematic search. After removing the duplicates, 824 articles remained for title and abstract screening. Subsequently, 20 articles were selected for full-text review, of which 11 studies met the eligibility criteria and were included in the systematic review and meta-analysis [5–7, 9–15]. Figure 1 illustrates the PRISMA flow diagram. The results of the JBI Critical Appraisal quality assessment are presented in Supplementary Table 2.

Characteristics of included studies

Characteristics of studies evaluating ROP prevalence by vitamin D status (Sufficient vs. deficient)

Table 1 summarizes the findings of the six included studies that reported serum vitamin D levels in both the ROP and control groups [5–7, 9–11]. The publication years ranged from 2017 to 2025. Geographically, two studies were conducted in Iran [7, 11], two in India [6, 10], and one each in China [5] and Turkey [9]. The sample size of the ROP group ranged from 18 to 97, and in the healthy controls ranged from 16 to 162. The mean gestational age was 29.0 weeks in the ROP group and 30.6 weeks in the control group. The mean birth weight in the ROP and control groups was 1160.13 and 1384.38 g, respectively. Based on the meta-analysis results infants with ROP had significantly lower gestational age (MD = – 2.10 weeks, 95% CI: –2.56 to – 1.64, $p < 0.001$) and lower birth weight (MD = – 250.75 g, 95% CI: –384.98 to – 116.53, $p < 0.001$) (Supplementary Fig. 4) compared to the control group. Heterogeneity was moderate for gestational age (I^2 = 36.57%) but high for birth weight (I^2 = 81.03%) (Supplementary Fig. 5).

The study by Mosayebi et al. 2025 [11] only compared serum vitamin D levels between treatment-requiring ROP and non-treatment-requiring ROP groups.

Characteristics of studies evaluating ROP prevalence by vitamin D status (Sufficient vs. deficient)

Table 2 reports the characteristics of studies investigating the prevalence of ROP according to vitamin D status (deficient vs. sufficient) [12–16]. Five studies published between 2015 and 2025 from Ireland [12], Korea [13], Turkey [14], Iran [16], and China [15] were included. The sample size varied from 29 to 150 in the vitamin D-deficient group and 12 to 111 in the vitamin D-sufficient group. The mean gestational age was 29.43 weeks in the vitamin D-deficient infants and 29.76 weeks in the vitamin D-sufficient infants. C. Onwuneme et al. 2015 [12], Barzegar et al. 2025 [16], and E. Koc et al. 2022 [14] did not report a statistically significant difference in ROP risk between the deficient and sufficient groups. In contrast, the results from Kim et al. 2019 [13] and Gou et al. 2024 [15] indicated that infants with vitamin D deficiency had a higher risk of developing ROP.

Meta-analysis of mean vitamin D level: ROP vs. control

The analysis of five studies, comprising 281 infants with ROP and 287 control infants, revealed a significantly lower vitamin D level in the ROP group (SMD: -0.94, 95% CI: -1.21 to -0.67; I^2 = 48.26%, p-value < 0.001), as shown in Fig. 2 [5–7, 9, 10]. Heterogeneity was not statistically significant (p-value for heterogeneity = 0.1). In the leave-one-out sensitivity analysis, the results remained statistically significant (p-value < 0.05) after the sequential removal of each study (Figure S1).

Subgroup analysis based on the timing of vitamin D measurement showed that infants with ROP had significantly lower vitamin D levels compared to controls, both at 1–3 days after birth [7, 9, 10] (SMD: -1.16, 95% CI: -1.41 to -0.90; I^2 = 0.00%, $p < 0.001$) and at 4 weeks after birth [5, 6] (SMD: -0.66, 95% CI: -0.93 to -0.39; I^2 = 0.00%, $p < 0.001$). Furthermore, vitamin D levels were significantly lower in the first 1–3 days after birth compared to

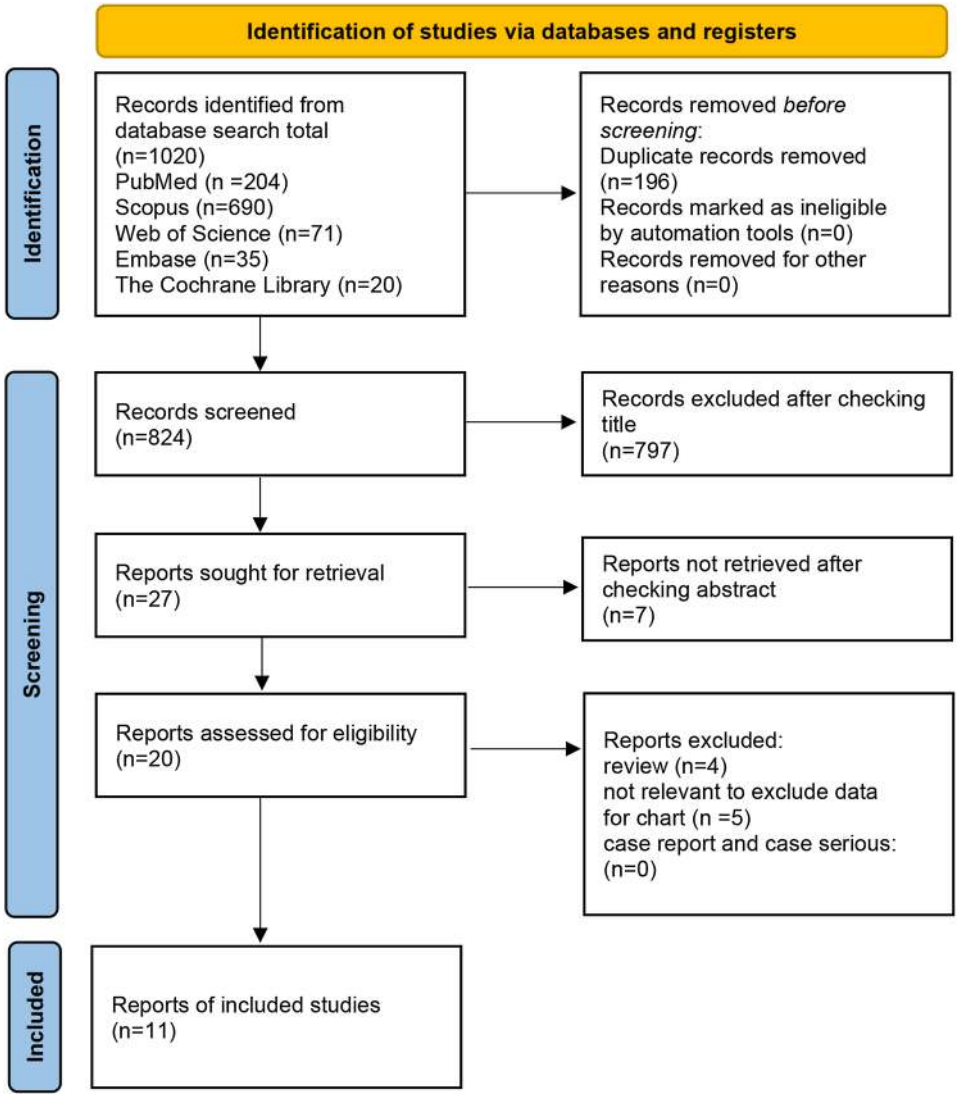

Fig. 1 The PRISMA flow diagram of the study selection process

levels at 4 weeks (p-value for subgroup difference = 0.01) (Fig. 3).

Meta-analysis of mean vitamin D level: treatment-requiring ROP vs. monitoring

The mean vitamin D level was compared between 49 infants with treatment-requiring ROP and 152 infants with non-treatment-requiring ROP (monitoring group). Infants requiring treatment had significantly lower vitamin D levels compared to the monitoring group (SMD: -0.90, 95% CI: -1.75 to -0.04; I^2 = 84.37%, p-value = 0.04) [5, 9, 11] (Fig. 4).

Pooled odds ratio for ROP in vitamin D deficient infants

Three studies, including 258 vitamin D-deficient infants and 221 vitamin D-sufficient infants, were included in this analysis [12–14]. The study by C. Onwuneme et al. 2015 [12] and I. Kim et al. 2019 [13] reported the lowest and highest odds ratios, respectively (OR: 1.11, 95% CI: 0.03 to 2.24 and OR: 3.24, 95% CI: 1.79 to 4.69). Overall, infants with vitamin D deficiency had a higher risk of ROP (OR: 6.69, 95% CI: 1.65 to 27.4, p = 0.01) (Fig. 5). In the sensitivity analysis, the results remained statistically significant ($p < 0.05$) after removing any single study (Figure S2).

Meta-regression and publication bias

Although the funnel plot showed visual asymmetry (Figure S3), Egger's test was not statistically significant (z = -0.30, p-value = 0.077), suggesting no strong evidence of publication bias. This discrepancy may arise because funnel plot asymmetry can stem from heterogeneity (e.g., varying study designs, populations) or true effect size variation rather than missing studies.

Table 1 Characteristic data of the included studies evaluation the serum vitamin D level in ROP vs. control

Author, Year	Country	Longitude, latitude	Sample Size (Male)		Vit D Level (ng/mL)		Mean Gestational Age (weeks)		Mean Birth Weight (grams)		Vit D deficiency level	Vit D method	Vit D assessment	Screening time for ROP
			ROP	Control	ROP	Control	ROP	Control	ROP	Control				
E.U. Kabatas, (9)2017	Turkey	39.9334° N, 32.8597° E	71(31)	26(9)	10.7 ± 6.5	17.9 ± 7.5	28.1 ± 2.1	30.7 ± 0.4	1068 ± 265	1455 ± 143	≤ 16 ng/mL	RIS	First 3 days after birth	4 weeks after birth
N. Srinivas(10), 2017	India	9.9312° N, 76.2673° E	30(NR)	16(NR)	15.7 ± 11	26 ± 6.5	NR	NR	NR	NR	< 20 ng/mL	CLIA	First day after birth	2–3 weeks after birth
H. Boskabad(7), 2022	Iran	32.4279° N, 53.6880° E	98(50)	56(24)	11.4 ± 6.5	22.3 ± 11.4	30.5 ± 2.2	32.05 ± 1.9	1334.58 ± 353.85	1491.87 ± 382.8	≤ 10 ng/mL	ELISA	First day after birth	4–6 weeks after birth
D Deb(6), 2022	India	13.0843° N, 80.2705° E	27(NR)	27(NR)	29.2 ± 11.1	42 ± 19.8	27 ± 1.7	28.9 ± 2.2	819.4 ± 227.1	910.4 ± 356.8	NR	NR	4 weeks after birth	4 weeks
X.Yin(5), 2024	China	36.0662° N, 120.3830° E	55(28)	162(90)	11.1 ± 4.31	14.2 ± 5.07	27.9 ± 2.1	30.2 ± 1.6	983.33 ± 207.56	1316.67 ± 333.5	NR	NR	4–6 weeks after birth	4–6 weeks after birth
Z. Mosayebi(11), 2025[1]	Iran	32.4279° N, 53.6880° E	18(9)	57(27)	27 ± 13	30 ± 12	28 ± 1	30 ± 1	1114 ± 297	1439 ± 470	< 20 ng/mL	ELISA	First day after birth	4–6 weeks after birth

Abbreviations: ROP: Retinopathy of prematurity, Vit D: Vitamin D, ELISA: Enzyme-linked immunoassay, RIA: Radioimmunoassay, CLIA: Chemiluminescent immunoassay, NR: Not Reported, N: North, E: East, ng: Nanogram, mL: Milliliters

1 The Mosayebi et al. 2025 compared the ROP-required treatment and ROP-not-required treatment

Table 2 Characteristic data of the included studies evaluating the prevalence of ROP in the deficient and sufficient vitamin D groups

Author, Year	Country	Total Sample (Male)		Mean gestational age (weeks)		Mean birth weight (grams)		ROP		Vit D Level		Vit D method	Finding
		D group	S group	D group	S group	D group	S group	D group	S group	D group	S group		
C. Onwuneme(12), 2015	Ireland	60(28)	60(28)	28.6 ± 2.3	29.1 ± 1.71	1171 ± 363	1229 ± 398	11	5	NR	NR	CLIA	No statistically significant difference.
I. Kim(13), 2019	Korea	150(84)	38(15)	28.39 ± 3.25	29.1 ± 2.5	1068.9 ± 295.6	1245.7 ± 267.1	38	2	9.6 ± 5.2	28.2 ± 7.2	UPLC–MS/MS and CLIA	An increased risk of ROP in Vit D deficiency.
E.Koc(14), 2022	Turkey	48(27)	12(7)	30.4 ± 1.9	31.3 ± 1.2	1555 ± 391	1840 ± 294	14	1	NR	NR	Competitive immunoassay	No statistically significant difference.
Y.Guo(15), 2024	China	119(71)	111(53)	30.14 ± 28.43	29.57 ± 28.0	1200 ± 950	1210 ± 1000	NR	NR	16.1 ± 13.5	23.8 ± 21.8	LC–MS/MS	An increased risk of ROP in Vit D deficiency.
H Barzegar(16), 2025	Iran	29 (NR)	15 (NR)	30.24 ± 1.6	31 ± 1.9	1280.9 ± 290.5	1404.3 ± 270	2	0	NR	NR	HPLC	No statistically significant difference.

Abbreviations: ROP: Retinopathy of prematurity, Vit D: Vitamin D, CLIA: Chemiluminescent immunoassay, LC-MS/MS: Liquid chromatography-tandem mass spectrometry, UPLC-MS/MS: Ultra-performance liquid chromatography-tandem mass spectrometry, HPLC: High-performance liquid chromatography, NR: Not Reported, N: North, E: East, ng: Nanogram, mL: Milliliter, S group: Sufficient group, D group: Deficient group

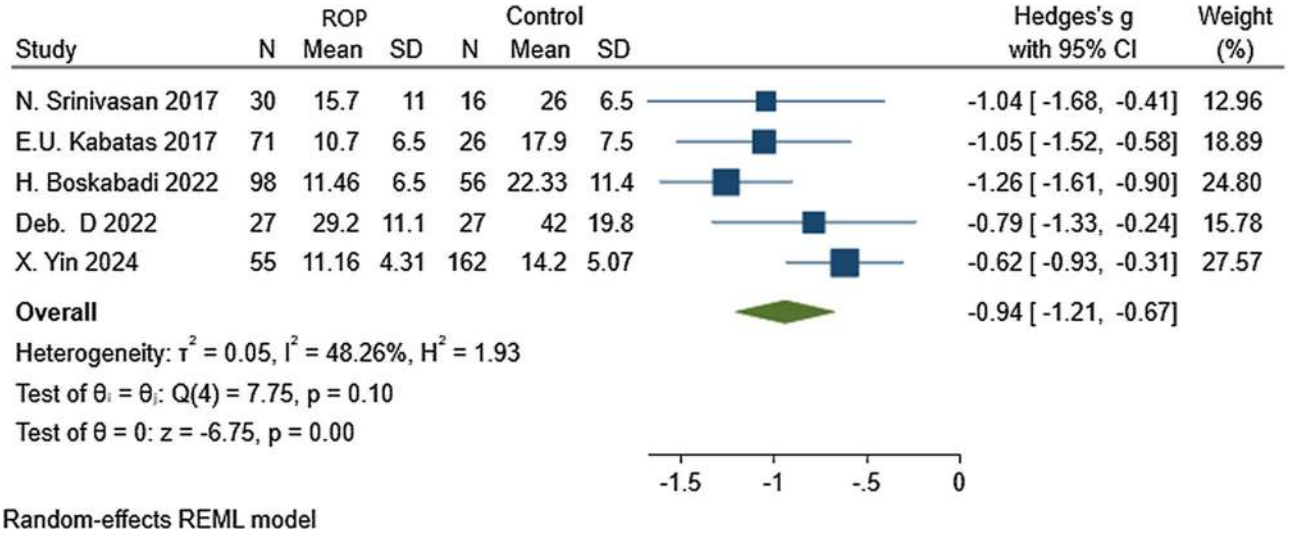

Fig. 2 Serum vitamin D levels in ROP infants compared to healthy controls

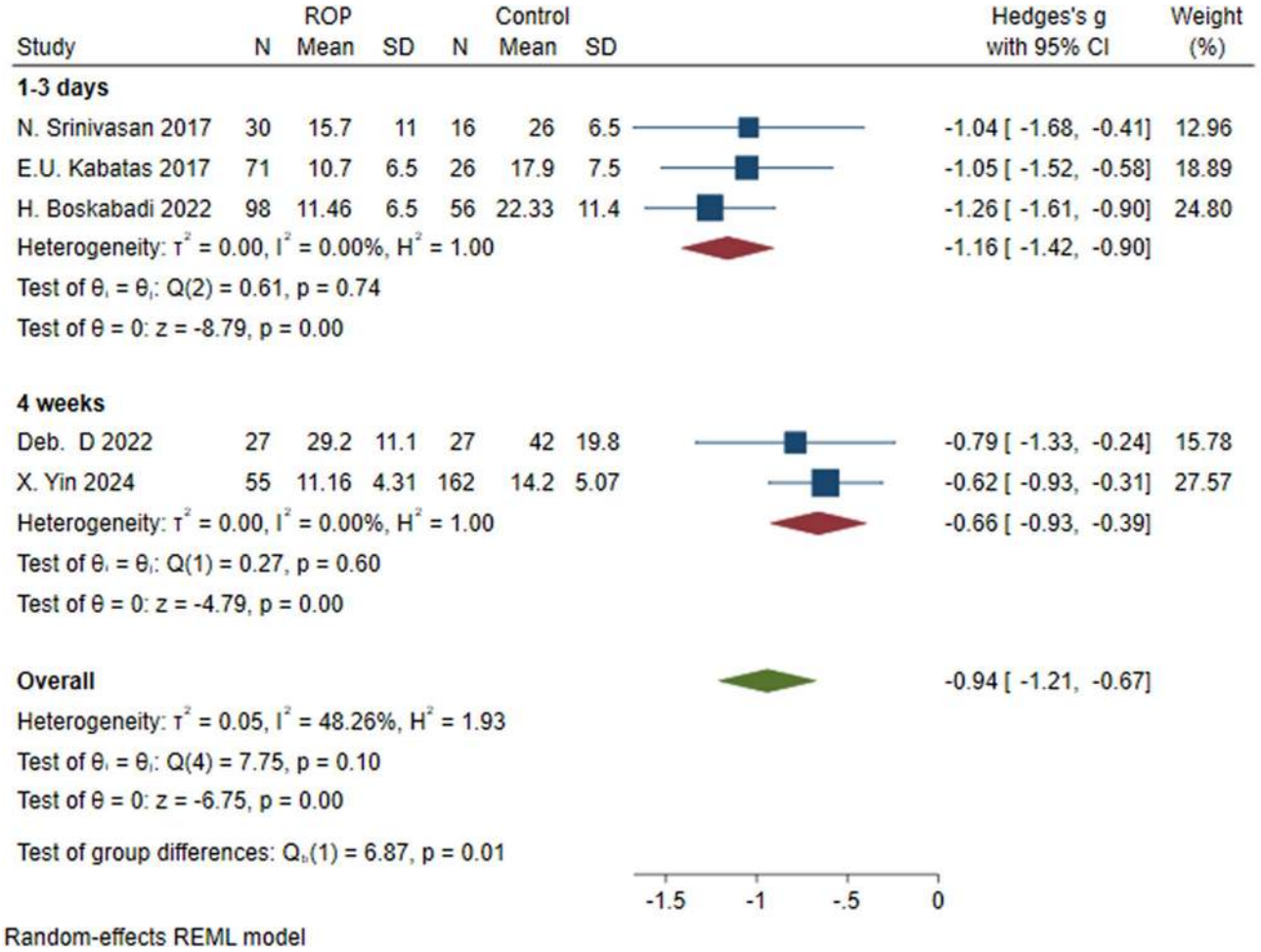

Fig. 3 Subgroup analysis of serum vitamin D levels in ROP infants compared to healthy controls by the time of vitamin D assessment

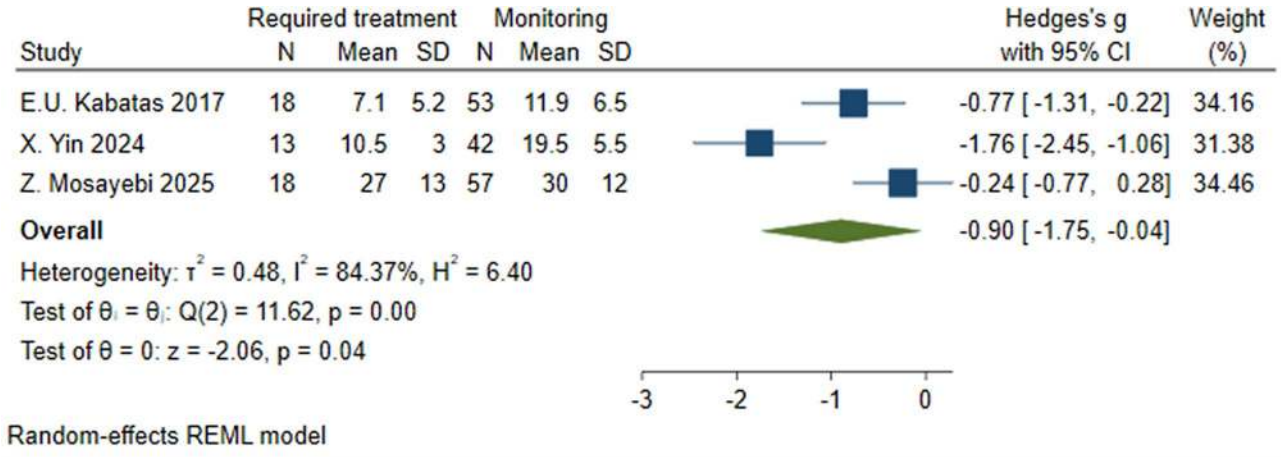

Fig. 4 Serum vitamin D levels in treatment-requiring ROP vs. monitoring

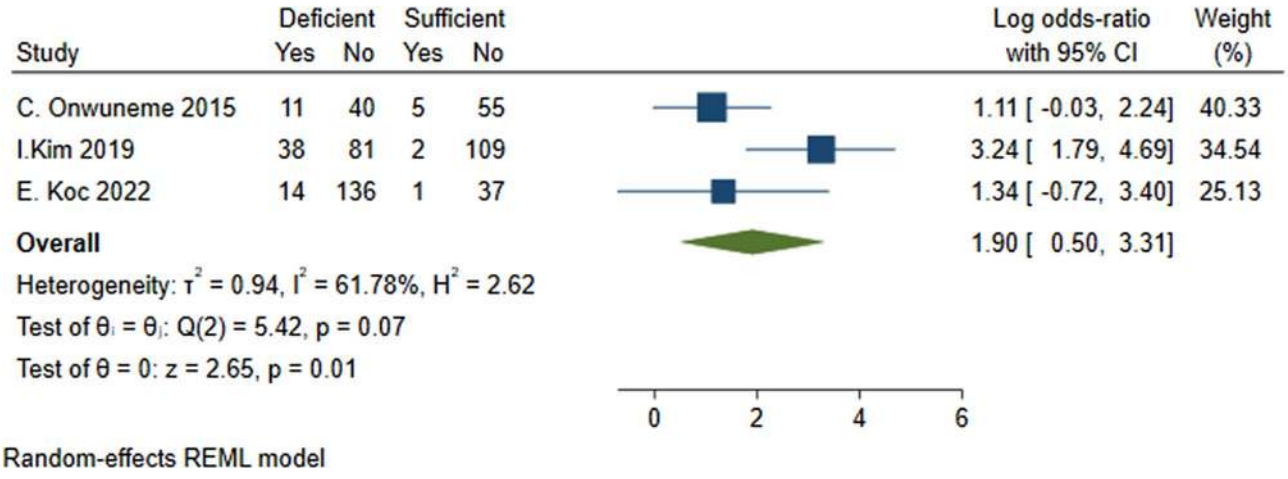

Fig. 5 Log Odds ratio of ROP in Vitamin D Deficient Infant. The scaled odds ratio by applying the exponential function (OR = exp (Log OR)) is (OR: 6.69, 95% CI: 1.65 to 27.4, $p = 0.01$)

Meta-regression results indicated that infants with lower birth weight had a greater difference in serum vitamin D levels compared to the control group (Coefficient: -0.0013, p-value = 0.043). Additionally, infants born in countries at higher latitudes had lower serum vitamin D levels (Coefficient: 0.007, p-value = 0.014). Meta-regression for birth weight and longitude was not statistically significant ($p > 0.05$) (Table S3).

Discussion

This study is a systematic review and meta-analysis evaluating the association between vitamin D and ROP. Six relevant studies, including 299 neonates with ROP and 378 control neonates, found that preterm infants who developed ROP had significantly lower serum vitamin D levels compared with controls [5–7, 9, 10]. This association was stronger for measurements within the first 1–3 days after birth [7, 9, 10] than at 4 weeks [5, 6]. Serum vitamin D levels in the first days after birth may better reflect fetal and maternal stores and could have a greater impact on the early stages of retinal development. In contrast, vitamin D levels at 4 weeks after birth are more likely to be influenced by nutritional intake, supplementation, or neonatal intensive care unit (NICU) interventions. This theory further highlights the importance of evaluating serum vitamin D levels in the early postnatal period. Additionally, infants with lower birth weight were at a higher risk of developing the disease. It may reflect reduced vitamin D stores and limited placental transfer in preterm infants. This declining association may be attributed to the maternal-fetal vitamin D transfer in the third trimester [9, 17].

Moreover, the analysis demonstrated a meaningful association between serum vitamin D levels and the latitude of the study locations (Coefficient: -0.0013, p-value = 0.043). With increasing latitude of the study location, the difference in serum vitamin D levels between the ROP and control groups became more pronounced. In

addition, infants with more severe ROP who required treatment had significantly lower serum vitamin D levels compared with those with milder ROP who were only monitored. These findings suggest that vitamin D deficiency may contribute to the progression of ROP requiring medical intervention. This observation aligns with previous studies highlighting the role of vitamin D in angiogenesis [4, 18–20] and in the inflammatory processes underlying ROP [19, 20].

Several biological mechanisms have been proposed to explain vitamin D's multifaceted role in retinal cells. Active vitamin D metabolites exhibit anti-angiogenic, anti-inflammatory, and antioxidant properties [21]. Vitamin D strongly inhibits angiogenesis in two cell types, including retinal pericytes and endothelial cells. As pericyte cells have higher vitamin D receptors (VDR) than endothelial cells [7], they have a stronger effect by inhibiting pericyte proliferation, migration, and arresting their cell cycle in the G_0/G_1 phase [9, 20]. On the other hand, vitamin D tends to increase VEGF, a protein involved in healthy angiogenesis, which induces interaction between VEGF-R2 and PDGF-Rβ receptors, resulting in attenuation of angiogenesis signals and preventing abnormal angiogenesis [19, 20]. In the presence of vitamin D, suppression of angiogenic mediators such as VEGF, IL-8, and matrix metalloproteinases 2 and 9 occurs [9, 22].

Additionally, vitamin D deficiency is associated with retinal neovascularization, abnormal vessel development, and even blindness [4]. Previous studies have highlighted the role of vitamin D in diabetic retinopathy, suggesting that it may delay the onset and progression of the disease by reducing pro-inflammatory proteins (e.g., interleukin-6, tumor necrosis factor-α), oxidative stress, and retinal angiogenesis. Therefore, vitamin D supplementation has been recommended to lower the risk of retinal damage, although its therapeutic efficacy remains uncertain [23, 24]. Studies by Jamali et al. 2017 [20] and Murugeswari et al. 2023 [4] demonstrated that vitamin D supplementation increases VEGF levels during the early stages of ROP, thereby supporting normal vascularization and physiologic vessel proliferation. At the same time, vitamin D appears to exert anti-angiogenic effects under hypoxic conditions, helping prevent pathological and uncontrolled neovascularization [20]. Furthermore, neonates deficient in vitamin D require a significantly longer period of oxygen therapy than those with sufficient vitamin D levels, a well-known risk factor for the development of retinopathy [16, 25].

The variations in the techniques employed to measure serum vitamin D levels among the included studies may also be the cause of the heterogeneity observed in our meta-analysis. Four studies have reported the prevalence of vitamin D insufficiency, including two by by Onwuneme et al. 2015 [12] and E. Koc et al. 2022 [14] reported no statistically significant difference in ROP incidence between vitamin D-deficient and sufficient groups. They measured vitamin D using a chemiluminescent immunoassay (CLIA) and a competitive immunoassay, respectively. In comparison, other studies by Kim et al. 2019 [13] and Gou et al. 2024 [15] utilized a spectrometry-based method. As this method has higher accuracy and specificity [26], the results of these studies are less prone to measurement bias. Moreover, the various cut-offs for vitamin D deficiency in preterm neonates across studies ranged from ≤ 10 ng/mL [11, 12] to ≤ 20 ng/mL [10, 13] or ≤ 30 ng/mL [10, 13], which tends to make comparisons between studies difficult.

Our study has several limitations that should be considered. First, there is a lack of detailed reporting and analysis of maternal serum vitamin D levels, despite the strong association between maternal and neonatal vitamin D levels. Second, there was considerable heterogeneity in the methods used to measure serum vitamin D levels across studies, which may affect the comparability of results. Another limitation of our research is the application of different definitions and cut-off values for vitamin D deficiency. This makes it difficult to draw consistent conclusions. Additionally, the timing of blood sampling for vitamin D assessment was inconsistent across studies, potentially introducing bias. Fourth, in many studies, patients were not categorized by disease severity, limiting the ability to assess relationships. Finally, potential confounding factors, such as the duration of NICU stay, specifically the oxygen therapy period, as well as other clinical variables, were not adequately controlled in several studies.

Conclusion

The findings of the current study suggest that vitamin D status may be associated with the risk and severity of ROP in preterm infants. However, the available evidence does not establish a causal relationship or demonstrate that vitamin D supplementation prevents ROP. Further well-designed prospective studies are needed to determine whether vitamin D status has an independent role in ROP and whether supplementation provides clinical benefit.

Abbreviations

ROP	Retinopathy of prematurity
SMD	Standardized mean difference
OR	Odds ratio
VEGF	Vascular endothelial growth factor
PROSPERO	Prospectively registered in the International Prospective Register of Systematic Reviews
VDR	Vitamin D receptors
CLIA	Chemiluminescent immunoassay
NICU	Neonatal intensive care unit

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40942-026-00930-2.

Supplementary Material 1

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None.

Author contributions
EF and MP contributed to the study design. EF and AD performed the data extraction. EF and AD inscribed the primary draft of the manuscript. MP, MM, AMA, and EF revised the manuscript. EF conducted the meta-analysis. MP and EF amended the manuscript, and all authors revised it critically and have approved the final version.

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Data availability
The data used to support the findings of this study are available from the corresponding author upon request.

Code availability
Not applicable.

Declarations

Ethical approval
Not applicable.

Consent for publication
Not applicable.

Consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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