ORIGINAL ARTICLE

The best type of probiotic for the prevention and treatment of neonatal physiological jaundice: A systematic review and meta-analysis

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Background: Gut microbiota play an important role in bilirubin metabolism and may influence the course of neonatal physiological jaundice. This systematic review and meta-analysis aimed to evaluate the strain-specific efficacy of probiotics in the prevention and adjunctive treatment of neonatal physiological jaundice. **Materials and Methods:** A comprehensive search of PubMed, Scopus, Embase, Web of Science, Google Scholar, Cochrane Library, World Health Organization databases, and Persian databases (Scientific information database [SID] and Magiran) for studies published up to 2024 was conducted. Randomized controlled trials (RCTs) evaluating probiotics in term and late-preterm neonates (≥35 weeks) with physiological jaundice were included. Data extraction, quality assessment, and meta-analysis were performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines using a random-effects model. **Results:** Nineteen RCTs (13 therapeutic and 6 prophylactic) were included. Prophylactic probiotic administration was associated with a reduced need for phototherapy (odds ratio [OR] =0.60; 95% confidence interval [CI]: 0.37–0.96). As an adjunct to phototherapy, probiotics were associated with lower bilirubin levels (mean difference [MD] = −1.61; 95% CI: −3.10–−0.11), shorter phototherapy duration (~5 h), and reduced hospitalization (0.3 days). Reduction in bilirubin was more evident during the 2nd and 3rd days of treatment. Strain-specific differences were observed; *Clostridium butyricum* and *Lactobacillus reuteri* demonstrated larger pooled effect sizes for bilirubin reduction, whereas *Saccharomyces boulardii* showed greater protective effect against phototherapy. **Conclusion:** Probiotics may serve as beneficial adjuncts in the prevention and management of neonatal physiological jaundice, with potential strain-dependent differences. Given heterogeneity and limited data for some strains, findings should be interpreted cautiously. Further well-designed, adequately powered RCTs are warranted.

Key words: Hyperbilirubinemia, infant, jaundice, neonatal, newborn, phototherapy, probiotics

How to cite this article: Barekatain B, Asefi Z, Kelishadi R, Yazdi M, Heidari-Beni M. The best type of probiotic for the prevention and treatment of neonatal physiological jaundice: A systematic review and meta-analysis. J Res Med Sci 2026;31:21.

INTRODUCTION

Neonatal jaundice is one of the most common conditions requiring medical attention during the 1st week of life, affecting approximately 60% of term and 80% of preterm infants. A key step in bilirubin metabolism occurs in the intestine, where gut microbiota convert bilirubin into urobilinogen.[1-3] Neonates are born with a sterile gut and limited beneficial bacteria, impairing this pathway, which accounts for approximately 60% of bilirubin excretion. Intestinal colonization begins immediately after birth, particularly during vaginal delivery, transferring beneficial bacteria such as *Bifidobacterium* and *Clostridia* from the mother.[4,5] Intestinal bacteria play dual roles in bilirubin metabolism: Some produce beta-glucuronidase, enhancing enterohepatic circulation

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jrms

DOI: 10.4103/jrms.jrms_746_25

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Submitted: 13-Jul-2025; **Revised:** 22-Feb-2026; **Accepted:** 27-Apr-2026; **Published:** 28-Aug-2026

and raising bilirubin levels, whereas others convert bilirubin to urobilinogen, facilitating its excretion. Recent studies have investigated the mechanisms of different probiotic strains, which may influence bilirubin metabolism in neonates. The distinct mechanisms of each strain suggest that probiotics could have varying effects on the severity and duration of neonatal jaundice.[6] Probiotics can help restore this balance by promoting beneficial bacteria, modulating gut pH, and improving bowel motility, thereby potentially reducing jaundice.[7,8]

Clinical studies suggest that probiotics are effective adjuncts to phototherapy, the standard treatment for neonatal jaundice, which converts unconjugated bilirubin into excretable forms.[9] For example, Chen *et al*. reported that adjunctive probiotic therapy in 1067 neonates significantly reduced serum bilirubin levels, shortened phototherapy duration, and decreased hospital stay without severe adverse events.[10] Similar benefits were observed in smaller studies by Liu *et al*., demonstrating reductions in bilirubin levels, phototherapy duration, and jaundice incidence in neonates receiving probiotics alongside standard care.[11]

Despite these promising results, the optimal probiotic strain for preventing and treating neonatal jaundice remains unclear due to differences in mechanisms, formulations, and study populations. Therefore, a comprehensive systematic review is needed to evaluate the effects of various probiotic strains and identify the most effective options for both prophylactic and therapeutic applications. The present study aims to assess the efficacy of different probiotic strains in neonates with physiological jaundice and determine the most effective strain for clinical use.

MATERIALS AND METHODS

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and Cochrane methodology to ensure methodological rigor and transparency.

Population, intervention, comparison, and outcomes framework

The study objectives and data extraction were structured according to the population, intervention, comparison, and outcomes (PICO) framework:

- Population (P): Term and preterm neonates (gestational age [GA] ≥35 weeks) under 1 month of age
- Intervention (I): Probiotic supplementation (various strains)
- Comparator (C): Standard care, including phototherapy without probiotics
- Outcomes (O): Total bilirubin, phototherapy requirement, duration of phototherapy, length of hospitalization, and adverse events.

Search strategy and study selection

A comprehensive systematic search was conducted in PubMed, Scopus, Embase, ISI Web of Science, Google Scholar, World Health Organization, Cochrane Library, and Persian databases, including SID and Magiran up to 2024. The reference lists of included articles were also screened to identify additional relevant studies. Keywords were selected based on MeSH terms and previous literature, and combined using Boolean operators ("AND" and "OR") with wildcard characters ("*") when appropriate to broaden the search.

The full search strategy is provided in Table 1.

Inclusion and exclusion criteria

Eligible studies were limited to human research conducted on term and late preterm neonates with a GA of ≥ 35 weeks who were younger than 1 month of age. Only randomized controlled trials (RCTs) investigating the effect of probiotic supplementation on neonatal jaundice were considered for inclusion. Studies published in English or Persian were eligible. Studies were excluded if they lacked sufficient data to permit quantitative synthesis, were rated as low quality according to the Joanna Briggs Institute (JBI) critical appraisal tools, or employed observational study designs.

After initial retrieval and screening, titles and abstracts were independently assessed by two researchers. Full texts of potentially eligible studies were reviewed, and disagreements were resolved by consensus or consultation with a third reviewer. Data extraction included study characteristics, population details, probiotic strains and dosages, follow-up duration, and outcomes.

A total of 19 studies published between 2014 and 2023 met the inclusion criteria (13 therapeutic, 6 prophylactic) and were included in the systematic review and meta-analysis. Figure 1 presents the PRISMA flow diagram of the study selection process.

Quality assessment of included studies

The quality of the included studies was systematically assessed using the standardized JBI critical appraisal tools. To ensure robustness, two independent researchers evaluated each study, and any discrepancies were resolved through discussion or consultation with a third expert. Only studies that met the predefined inclusion criteria and demonstrated acceptable methodological quality were included in the final analysis.

The risk of bias (ROB) was further evaluated using the original Cochrane ROB tool (first introduced in 2008 and

Table 1: Search strategy

pubmed	Search terms	Results	Magiran	Search Terms	Results
#1	((infant) OR newborn) OR Neonatal	875/064	#1	Neonatal, or Infant, or newborn	985
#2	"Jaundice"[Mesh] AND "Hyperbilirubinemia"[Mesh] AND "Bilirubin"[Mesh] AND "Jaundice, Neonatal"[Mesh] AND "Hyperbilirubinemia, Neonatal"[Mesh] AND "Jaundice, Obstructive"[Mesh] AND "Hyperbilirubinemia"[Mesh]	13	#2	total bilirubin or Icterus or Hyperbilirubinemia or physiologic neonatal jaundice	3642
#3	(((((((((probiotics) OR (Bifidobacterium Longum)) OR (Bifidobacterium Breve)) OR (Bifidobacterium Infantis)) OR (Lactobacillus Helveticus)) OR (Lactobacillus acidophilus)) OR (Lactobacillus reuteri)) OR (Lactobacillus plantarum)) OR (Lactobacillus rhamnosus)	4972	#3	probiotics or Bifidobacterium Longum or Bifidobacterium Breve or Bifidobacterium Infantis or Lactobacillus Helveticus	565
#4	neonatal OR infant OR newborn AND Jaundice OR icterus OR total bilirubin OR Hyperbilirubinemia AND probiotics	133	#5	Jaundice and probiotics and Neonatal	4
Cochrane			Web of science		
#1	(Neonatal, or Infant, or newborn):ti,ab,kw	1425	#1	((TI=(Infant)) OR TI=(Neonatal)) OR TI=(newborn)	349/067
#2	(Jaundice Neonatal):ti,ab,kw OR (total bilirubin):ti,ab,kw OR (Icterus):ti,ab,kw OR (Hyperbilirubinemia):ti,ab,kw OR (Icterus Gravis Neonatorum):ti,ab,kw	55	#2	((((TI=(Jaundice Neonatal)) OR TI=(total bilirubin)) OR TI=(Icterus)) OR TI=(Hyperbilirubinemia)) OR TI=(Icterus Gravis Neonatorum)	5/065
#3	(probiotic OR bifidobacterium longum OR bifidobacterium breve OR bifid bacterium infantis OR lactobacillus helveticus):ti,ab,kw OR (lactobacillus acidophilus):ti,ab,kw OR (lactobacillus reuteri):ti,ab,kw OR (lactobacillus plantarum):ti,ab,kw OR (lactobacillus rhamnosus):ti,ab,kw	71	#3	((((((((((TI=(probiotics)) OR TI=(Bifidobacterium Longum)) OR TI=(Bifidobacterium Breve)) OR TI=(Bifidobacterium Infantis)) OR TI=(Lactobacillus Helveticus)) OR TI=(Lactobacillus acidophilus)) OR TI=(Lactobacillus reuteri)) OR TI=(Lactobacillus plantarum))) OR TI=(Lactobacillus rhamnosus)	23/913
#1 and #2 and #3	((infant or Neonatal or newborn) and (probiotic or bifidobacterium longum OR bifidobacterium breve OR bifid bacterium infantis OR lactobacillus helveticus OR lactobacillus acidophilus OR lactobacillus reuteri OR lactobacillus plantarum OR lactobacillus rhamnosus) or Icterus*):ti,ab,kw	20	#4	#1 AND #2 AND #3	12
embase			scopus		
#1	icterus:ti OR jaundice OR hyperbilirubinemia	127557	#1	(TITLE-ABS-KEY (ifant) OR TITLE-ABS-KEY (newborn) OR TITLE-ABS-KEY (neonatal))	1899416
#2	"probiotic"/exp OR probiotic OR bifidobacterium:ti OR longum:ti OR "bifidobacterium breve":ti OR "bifid bacterium infantis":ti OR "lactobacillus helveticus":ti OR "lactobacillus acidophilus":ti OR "lactobacillus reuteri":ti OR "lactobacillus plantarum":ti OR "lactobacillus rhamnosus":ti	73337	#2	(TITLE-ABS-KEY (icterus) OR TITLE-ABS-KEY (jaundice) OR TITLE-ABS-KEY (hyperbilirubinemia))	103326
#3	"infant"/exp OR infant	1.483575	#3	(TITLE-ABS-KEY (probiotic) OR TITLE-ABS-KEY (bifidobacterium AND longum) OR TITLE-ABS-KEY (bifidobacterium AND breve) OR TITLE-ABS-KEY (bifidobacterium AND infantis) OR TITLE-ABS-KEY (lactobacillus AND helveticus) OR TITLE-ABS-KEY (lactobacillus AND acidophilus) OR TITLE-ABS-KEY (lactobacillus AND reuteri) OR TITLE-ABS-KEY (lactobacillus AND plantarum) OR TITLE-ABS-KEY (lactobacillus AND rhamnosus))	109763
#4	#1 AND #2 AND #3	79	#4	#1 AND #2 AND #3 ((TITLE-ABS-KEY (probiotic) OR TITLE-ABS-KEY (bifidobacterium AND longum) OR TITLE-ABS-KEY (bifidobacterium AND breve) OR TITLE-ABS-KEY (bifidobacterium AND infantis) OR TITLE-ABS-KEY (lactobacillus AND helveticus) OR TITLE-ABS-KEY	87

Contd...

Table 1: Contd...

pubmed	Search terms	Results	Magiran	Search Terms	Results
				(lactobacillus AND acidophilus) OR TITLE-ABS-KEY (lactobacillus AND reuteri) OR TITLE-ABS-KEY (lactobacillus AND plantarum) OR TITLE-ABS-KEY (lactobacillus AND rhamnosus))) AND ((TITLE-ABS-KEY (icterus) OR TITLE-ABS-KEY (jaundice) OR TITLE-ABS-KEY (hyperbilirubinemia))) AND ((TITLE-ABS-KEY (ifant) OR TITLE-ABS-KEY (newborn) OR TITLE-ABS-KEY (neonatal)))	
Google scholar					
#1	Neonatal or Infant or newborn and Jaundice or total bilirubin or Icterus or Hyperbilirubinemia and probiotics "Neonatal" and "Jaundice" and "probiotics"	400			
#2	Neonatal or Infant or newborn	1000			
#3	Jaundice or icterus or bilirubin	1000			
#4	Probiotics	1000			

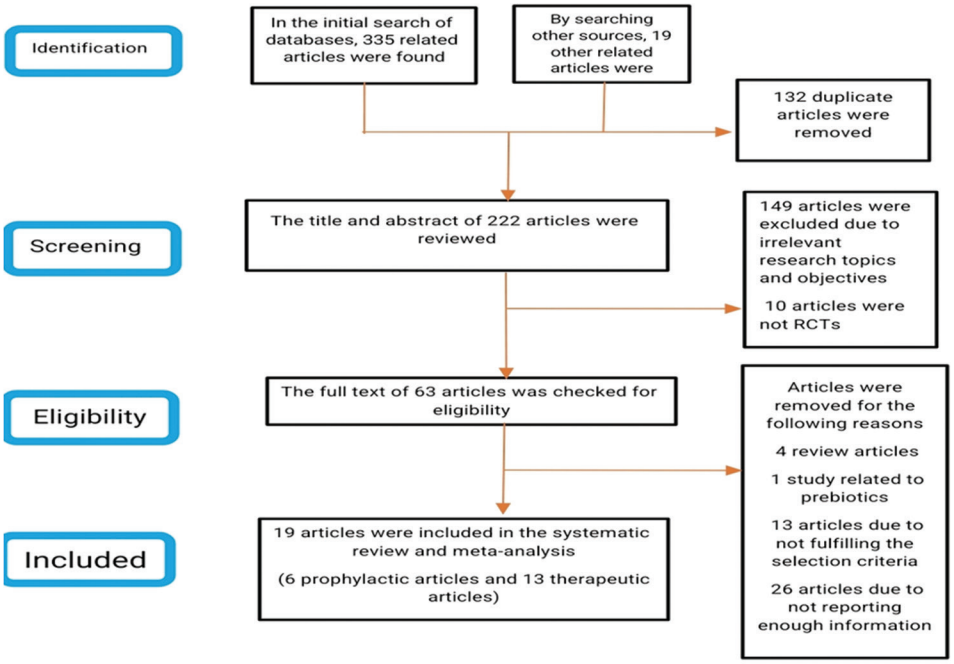

Figure 1: Steps of selecting and entering studies into meta-analysis

updated March 20, 2011). This tool assesses seven domains of potential bias in each study:

1. Random sequence generation- selection bias
2. Allocation concealment- selection bias
3. Blinding of participants and personnel- performance bias
4. Blinding of outcome assessment- detection bias
5. Incomplete outcome data- attrition bias
6. Selective reporting- reporting bias
7. Other sources of bias.

For each domain, studies were categorized as low risk, high risk, or unclear risk, ensuring a standardized and transparent evaluation of methodological quality across all included studies.[12] The detailed assessment for each study is summarized in Table 2 in appendix, which has been reformatted into a traffic-light plot for clarity and ease of interpretation, in line with standard practices for systematic reviews and meta-analyses.

Risk of bias assessment

Assessment using the Cochrane ROB tool showed that most studies had a low ROB in allocation concealment, incomplete outcome data, and selective reporting. In contrast, random sequence generation and blinding domains demonstrated variable quality, with several studies rated as unclear or high risk. Overall, the

Table 2: E original Cocharne risk of bias toolTh

Author	Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Nouri S[12]	2022	Low	Low	Low	Low	Low	Low	Unclear
Serce O[13]	2014	Low	Low	Low	Low	Low	Low	Low
Andina Rezk D[14]	2023	Low	Low	Low	Low	Low	Low	High
Eghbalian F[15]	2023	High	Low	High	High	Low	Low	Unclear
Eghetaghi *et al.*[16]	2018	High	Unclear	Unclear	Unclear	Low	Low	Unclear
Waheed A[17]	2024	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Pasha Y[18]	2017	High	Low	Low	Low	Low	Low	Low
Chenarani R[19]	2022	Low	Low	Low	Low	Low	Low	Unclear
Torkaman M[20]	2017	Low	Low	Low	Low	Low	Low	High
Mutlu M[21]	2018	Unclear	Unclear	Unclear	Unclear	Low	Low	High
KE G[22]	2021	H	Unclear	Unclear	Unclear	Low	Low	High
Santosa I[23]	2022	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Babaie E[24]	2023	Unclear	Low	Low	Low	Low	Low	Unclear
Ahmadipour Sh[25]	2019	High	Low	Unclear	Unclear	Low	Low	Unclear
Tariq B[26]	2021	High	Low	Unclear	Unclear	Low	Low	Low
Chandrasekhar J[27]	2017	High	High	High	High	Low	Low	Low
Sughanti V[28]	2017	High	High	Unclear	Unclear	Low	Low	Low
Teran CG[29]	2021	High	Unclear	Unclear	Unclear	Low	Low	Low
Tsai ML[30]	2022	Low	Low	Low	Low	Low	Low	Unclear

predominance of low risk in outcome-related domains indicates an acceptable methodological quality of the included studies.

In summary, although certain domains - particularly random sequence generation and blinding - demonstrated high or unclear ROB in some studies, the overall methodological quality of the included trials was acceptable. The predominance of low risk in outcome-related domains supports the reliability of the pooled findings. Nevertheless, these limitations should be considered when interpreting the results, and future RCTs with improved reporting of randomization and blinding procedures are warranted.

Data extraction

Data extraction was performed independently by two researchers (Dr. Behzad Barekatein and Dr. Zahra Asefi). In case of discrepancies, consensus was reached through discussion, or a third reviewer (Dr. Maryam Yazdi) was consulted.

The full texts of included studies were reviewed, and data were systematically extracted using a predefined checklist, with reference to the PICO framework to ensure capture of relevant study information. The characteristics of the reviewed studies are presented in Table 3.

All extracted data were compiled into structured tables for analysis and interpretation. These tables contained the following details: Basic study information (e.g., author, year, and study type), number of neonates involved, type of intervention and dosage, follow-up duration, and study outcomes.

Primary outcomes included: Mean serum bilirubin, phototherapy requirements, duration of phototherapy, length of hospitalization, and reported adverse effects.

Statistical analysis

For binary outcomes, such as need for phototherapy, the odds ratio (OR) and 95% confidence intervals (CIs) were calculated for each study as the measure of effect size. For continuous outcomes, including hospitalization duration, phototherapy duration, the prophylactic effect of probiotics on the need for phototherapy, the preventive effect of probiotics on jaundice, the preventive effect of probiotics on bilirubin levels, and the effect of probiotics on bilirubin levels (mg/dL) after hospitalization for phototherapy, analyses were performed.

The mean and standard deviation after intervention in both the control and probiotic groups were extracted. The mean difference (MD) was used as the effect size. A random-effects model was applied to calculate the overall effect size. Heterogeneity across studies was assessed using the I^2 statistic. Subgroup analyses were performed based on probiotic type and follow-up days. Publication bias was not assessed, as the number of studies for specific outcomes was fewer than ten. Meta-analysis was conducted using Stata 17 (Stata 17 statistical software is developed and owned by StataCorp LLC.), with a two-tailed significance level of 0.05 applied to all analyses.

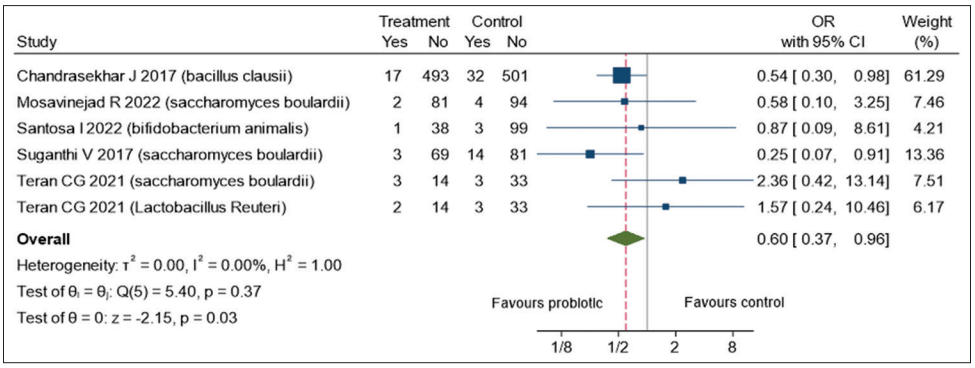

Figure 2: Forest plot for the odds ratio and 95% confidence interval of the need for phototherapy probiotics group compared to control

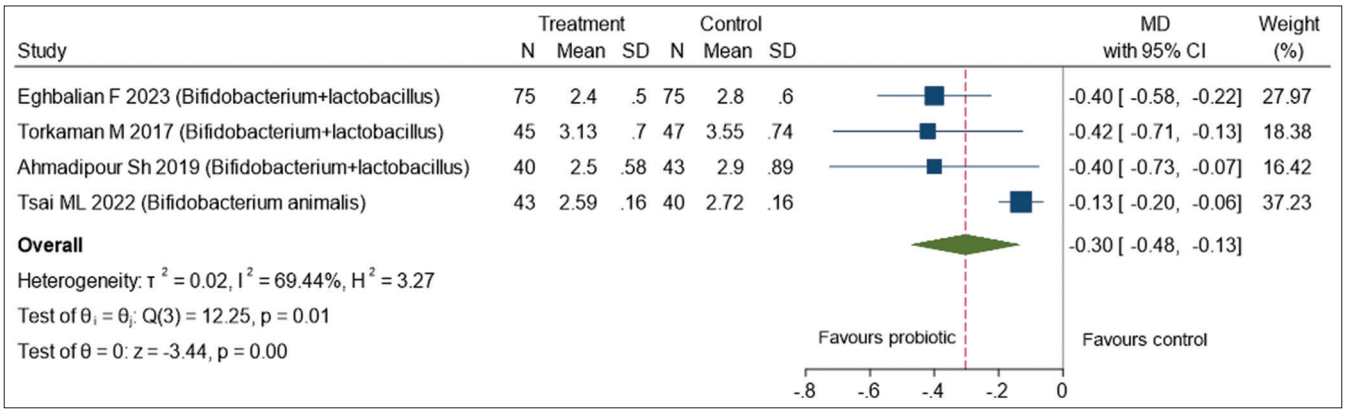

Figure 3: Forest plot for the mean difference of length of hospitalization in the probiotics group compared to control

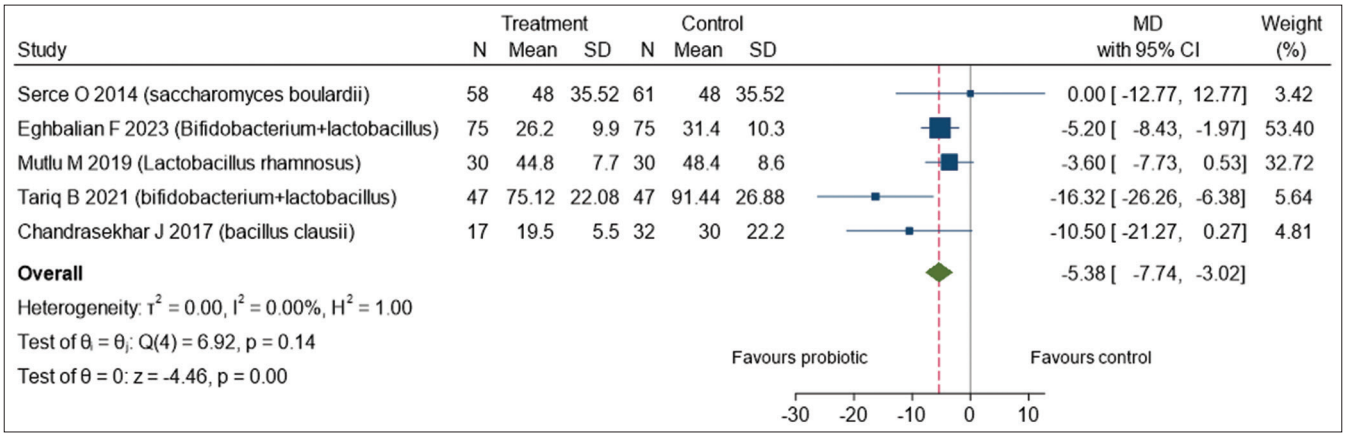

Figure 4: Forest plot for mean difference of phototherapy duration (hour) in the probiotics group compared to control

RESULTS

Effect of probiotics on the need for phototherapy

A pooled analysis of five studies revealed that probiotic consumption significantly reduced the need for phototherapy, showing a protective effect (OR = 0.6, 95% CI: 0.37–0.96). This indicates that neonates receiving probiotics prophylactically were less likely to require phototherapy compared to the control group. Among the probiotic strains used, *Saccharomyces boulardii* appeared to provide the most substantial protective effect against the need for phototherapy [Figure 2].

Preventive effect of probiotics on bilirubin levels

A meta-analysis of two studies comparing bilirubin levels on the 5th day of life (mg/dL) did not show a significant effect of preventive treatment with probiotics. (MD = −1.55, 95% CI = −3.94, 0.84). A total of two studies were analyzed; in one of them, probiotics were effective in preventing jaundice, while in the second study, probiotics were not effective in prevention.

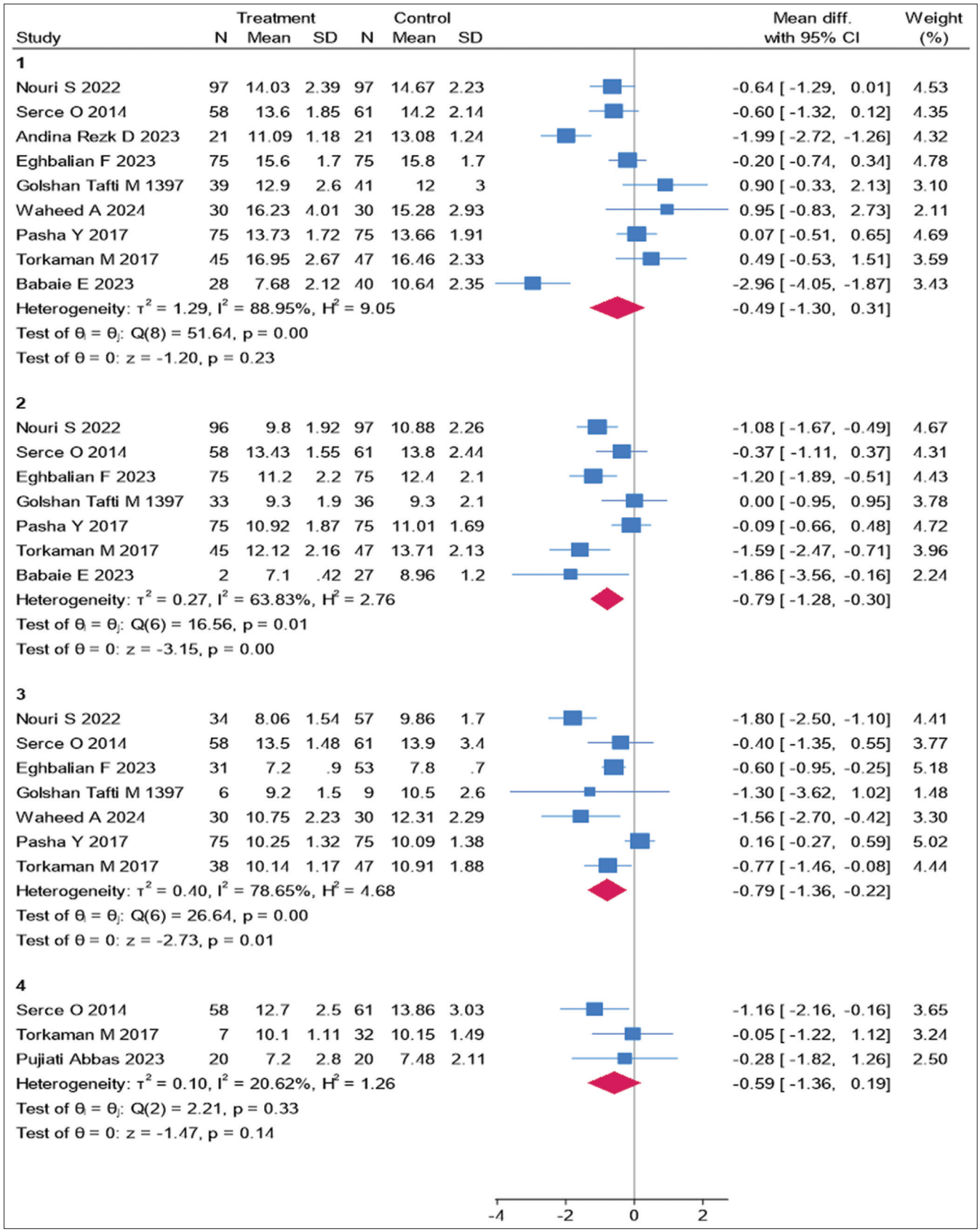

Figure 5: Forest plot for the mean difference of bilirubin level (mg/dL) on day 1, 2, 3, and 4 after hospitalization in the probiotic group compared to the control

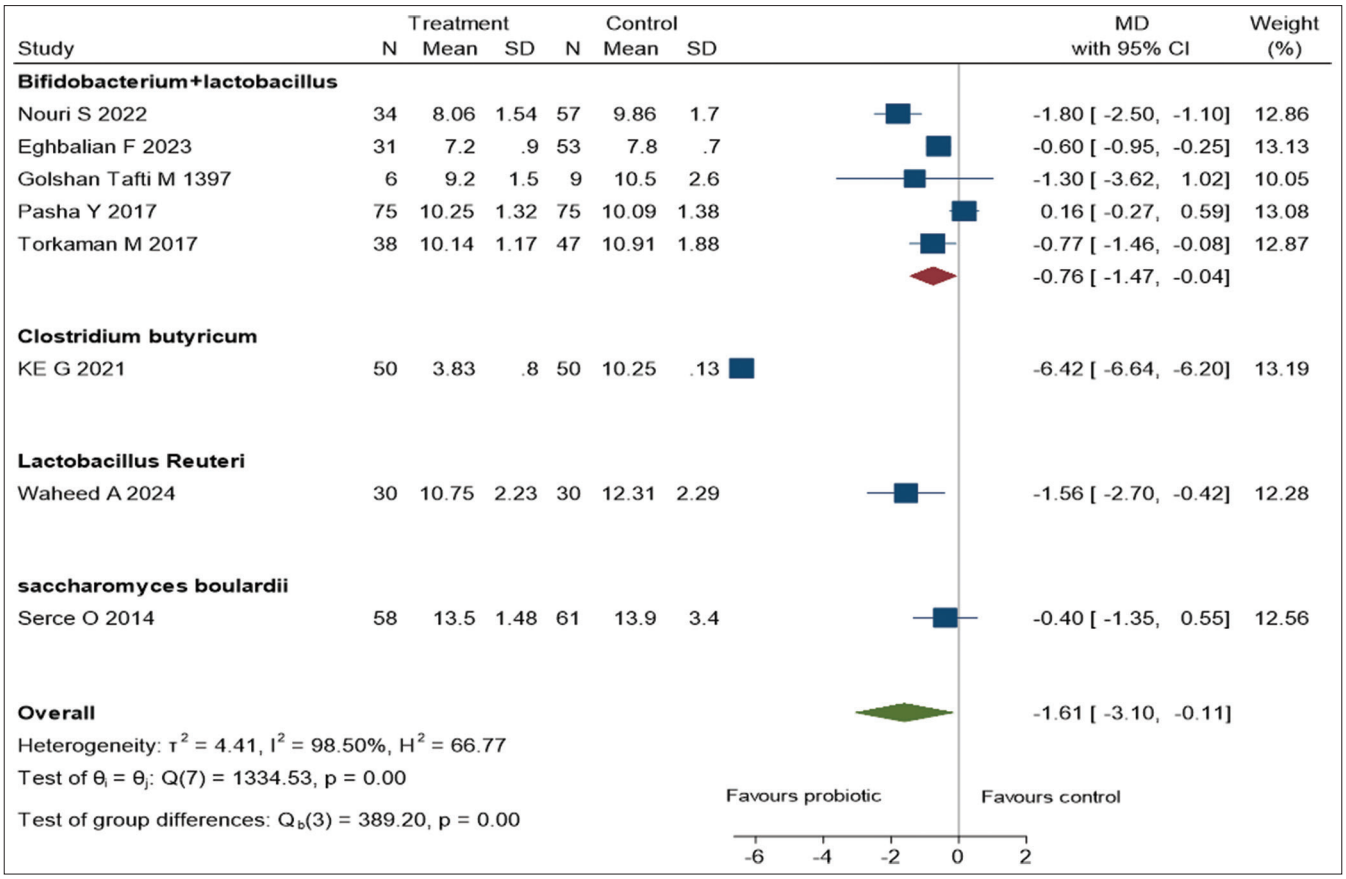

Figure 6: Forest plot for the effect of probiotic strains on bilirubin level (mg/dL) on the 3rd day of hospitalization

Effect of probiotics on hospitalization duration

A meta-analysis of four studies comparing hospitalization duration (days) demonstrated a significant reduction in the probiotic group compared to the control group (MD = −0.30, 95% CI: −0.48, −0.13) [Figure 3].

The combination of *Bifidobacterium* and *Lactobacillus* was particularly effective in reducing the length of hospital stay, showing greater efficacy than other probiotic interventions.

Effect of probiotics on phototherapy duration

A meta-analysis of four studies comparing phototherapy duration (hours) revealed that the probiotic group required approximately 5 h less phototherapy compared to the control group (MD = −5.38 h, 95% CI: −7.74, −3.02). The combination of *Bifidobacterium* and *Lactobacillus* was particularly effective in reducing phototherapy duration, showing the most significant impact among the probiotic interventions [Figure 4].

Effect of probiotics on bilirubin levels (mg/dL) after hospitalization for phototherapy

A total of 9 studies were conducted, in which infants with jaundice were divided into two groups. For the intervention group, in addition to phototherapy, probiotics were administered, whereas the control group in some studies received only phototherapy, and in other studies, the control group received a placebo in addition to phototherapy [Figure 5]. The mean and standard deviation of bilirubin levels (which were measured as serum bilirubin (mg/dL) in all included studies) were reported on different days. The results of the meta-analysis showed that the use of probiotics as an adjunct treatment led to a greater reduction in bilirubin levels on the second (MD = −0.79, 95% CI = −1.28, −0.30) and 3rd days (MD = −0.79 95% CI = −1.36, −0.22) of hospitalization. However, no significant effect was observed from the 4th day onward (MD = −0.65, 95% CI = −1.73, 0.44) [Figure 6].

There was no significant difference in the probiotics effect across follow-up days (P = 0.91). Consistently, the meta-regression analysis showed no significant association between follow-up day and the estimated probiotics effect (P = 0.244).

The effect of using different probiotic strains on bilirubin level

Figure 6 shows the effect of using different probiotic strains on the bilirubin level on the 3rd day of hospitalization. According to meta-analysis, probiotic consumption has a better effect in reducing bilirubin than placebo (MD = −1.61, 95% CI = −3.10, −0.11) and second, among the different probiotic strains, "*Clostridium butyricum*" strain (MD =

Table 3: Characteristics of included randomized controlled trials

Author	Year	Type of study	Location	Weight	Sample size	Intervention	Dose (drop)	Follow up time (day)
Nouri *et al*.[12]	2022	Double-blind clinical trial	Iran	>2500 g	194	*Bifidobacterium* + *lactobacillus*	5 drops	5
Serce *et al*.[13]	2015	Double-blind RCT	Turkey		119	*S. boulardii*	125 mg, 1 ml	4
Rezki *et al*.[14]	2023	Double-blind RCT	Indonesia	2500–4000 g	42	*L. reuteri*	5 drops	1
Eghbalian *et al*.[15]	2024	RCT (unblinded)	Iran	More than 2500 g	150	*Bifidobacterium* + *lactobacillus*	10 drop	3
Eghetaghi *et al*.[16]	1397	Clinical trials	Iran		80	*Bifidobacterium* + *lactobacillus*	5 drops	3
Waheed *et al*.[17]	2024	Quasi-experimental study	Pakistan		60	*L. reuteri*	5 drops	3
Zahed Pasha *et al*.[18]	2017	Double blinded randomized clinical trial	Iran	>2500 g	150	*Bifidobacterium* + *lactobacillus*	10 drops	3
Chenarani *et al*.[19]	2022	Triple blinded randomized clinical trial (prophylactic treatment)	Iran	More than 2500 g	196	*1010 S. boulardii*		5
Torkaman *et al*.[20]	2017	Randomized, controlled clinical trial	Iran	More than 2500 g	92	*Bifidobacterium* + *lactobacillus*	Half of a capsule of prokid	7
Mutlu *et al*.[21]	2018	Prospective placebo-controlled study (prophylactic treatment)	Turkey	Between the 10th and 90th percentiles	150	*L. rhamnosus*	5 drops	10
Ke *et al*.[22]	2021	RCT	Pakistan	Mean=3300 g	100	*C. butyricum*	420 mg twice a day	3
Santosa *et al*.[23]	2022	Control trial (prophylactic treatment)	Japan	Mean=3000 g	153	*B. animalis*	6 drop	5
Babaie *et al*.[24]	2023	Doubleblind, randomized, placebocontrolled clinical trial	Iran	More than 2500 g	80	*Bifidobacterium* + *lactobacillus*	5 drops	2/5
Ahmadipour *et al*.[25]	2019	RCT	Iran		83	*Bifidobacterium* + *lactobacillus*	5 drops	
Tariq *et al*.[26]	2021	RCT	Pakistan	>2500 g	94	*Bifidobacterium* + *lactobacillus*	Half of a capsule of prokid	
Chandrasekhar *et al*.[27]	2017	Open labeled clinical trial (prophylactic treatment)	India		510	*B. clausi*	The dose was 2000 million spores of multi antibioticresistant *B. clausii* per 5 ml at a dose of 2.5 ml twice a day	3
Teran *et al*.[28]	2021	RCT (prophylactic treatment)	Bolivia		98	*S. boulardi and L. reuterii* seperatley	One packet of Florest (200 mg in powder) and five drops of BioGaia	4
Suganthi and Das[29]	2016	RCT (prophylactic treatment)	India	More than 2.5 kg	181	*S. boulardii*	250 mg once a day for 2 days	3
Tsai *et al*.[30]	2022	Double-blind randomized trial	Taiwan		83	*B. animalis* subsp. *lactis CP-9*	2 capsules per day	

RCT=Randomized controlled trial; *B. animalis=Bifidobacterium animalis*; *S. boulardii=Saccharomyces boulardii*; *L. reuterii=Lactobacillus reuterii*; *B. clause=Bacillus clause*; *C. butyricum=Clostridium butyricum*; *L. rhamnosus=Lactobacillus rhamnosus*

−6.42, 95% CI = −6.64, −6.20) and then "*Lactobacillus reuteri*" strain (MD = −1.56, 95% CI = −2.70, −0.42) effect have been better in reducing the level of bilirubin, considering the small number of articles for these two probiotic strains, the quality and validity of these two articles were re-examined using the Cochrane tool, and the final results are reported in Table 2 in appendix.

The study by Ke *et al*.[22] has notable methodological limitations due to a high ROB in random sequence generation and the presence of other potential sources of bias; however, the management of outcome data and the reporting of results were adequate. The study by Tariq *et al*.[26] demonstrated a low ROB in outcome data management and selective reporting, the lack of transparent reporting of randomization and blinding methods resulted in an unclear ROB in the selection and performance domains.

DISCUSSION

Neonatal jaundice remains a common clinical condition with important social and economic implications. Identifying safe and effective adjunctive interventions to enhance bilirubin reduction and shorten phototherapy duration

is therefore clinically relevant. The present systematic review and meta-analysis synthesizes evidence from 19 RCTs involving term and late-preterm infants (≥35 weeks of gestation) with physiological jaundice and suggests that probiotics may confer beneficial adjunctive effects.

The pooled analysis indicates that probiotic supplementation alongside phototherapy is associated with a reduction in serum bilirubin levels, duration of phototherapy, and length of hospitalization. The effect on bilirubin reduction appeared more pronounced during the 2nd and 3rd days of phototherapy, with attenuation thereafter. Prophylactic administration reduced the likelihood of requiring phototherapy, although no significant reduction in bilirubin levels was observed in preventive settings. These findings suggest a potential supportive role of probiotics, particularly when used as adjunct therapy.

Strain-specific differences were observed. *C. butyricum* demonstrated the largest pooled effect size in bilirubin reduction, followed by *L. reuteri*. *S. boulardii* showed a comparatively greater reduction in the need for phototherapy, whereas combined *Bifidobacterium* plus *Lactobacillus* preparations were more effective in shortening hospitalization and phototherapy duration. However, these subgroup findings should be interpreted cautiously, as evidence for certain strains was derived from a limited number of trials and was accompanied by considerable heterogeneity.

The biological plausibility of probiotic efficacy may be explained by modulation of enterohepatic circulation. Recent studies have examined the mechanisms by which different probiotic strains influence bilirubin metabolism. Certain probiotic strains may reduce bilirubin reabsorption by enhancing intestinal motility, altering gut pH, and modifying microbial composition, thereby decreasing β-glucuronidase activity and limiting deconjugation of bilirubin.[6] These varying mechanisms may result in distinct effects on bilirubin metabolism.

Compared with earlier meta-analyses, including the 2017 review by Deshmukh *et al.*,[3] which included both term and preterm infants and cases of pathological jaundice, the present study applied stricter inclusion criteria by focusing exclusively on term and late-preterm infants with physiological jaundice. This narrower population likely improves internal validity and allows more targeted evaluation of strain-specific effects. Nevertheless, differences in study design, probiotic formulations, and outcome definitions may partly explain variations across reviews.

Regarding safety, no serious probiotic-related adverse events were reported. However, systematic reporting of adverse outcomes was inconsistent across trials. Therefore, the absence of reported complications should not be interpreted as definitive confirmation of safety.

Limitations

Several limitations should be acknowledged. First, many trials evaluated synbiotic or multistrain formulations rather than single-strain interventions, limiting precise attribution of strain-specific effects. Second, not all studies reported all predefined outcomes, restricting comprehensive quantitative synthesis. Third, small sample sizes and short follow-up periods may limit the detection of long-term outcomes. In addition, although restrictive inclusion criteria enhanced internal validity, they may reduce generalizability to infants < 35 weeks of gestation or those with pathological jaundice. Finally, formal assessment of publication bias was not feasible for several outcomes due to fewer than ten studies; therefore, potential publication bias cannot be excluded.

CONCLUSION

Current evidence suggests that probiotics may serve as beneficial adjuncts in reducing bilirubin levels, phototherapy duration, and hospitalization in term and late-preterm infants with physiological jaundice, with potential strain-dependent differences. However, given heterogeneity across studies and limited data for certain strains, findings should be interpreted with caution. Well-designed, adequately powered RCTs with standardized probiotic formulations and systematic safety reporting are warranted.

Acknowledgments

This study was conducted as part of research approved by Isfahan University of Medical Sciences. We would like to thank the university for its cooperation and for providing the necessary facilities to carry out this research. This study was approved by the Ethics Committee of Isfahan University of Medical Sciences with the ethics code IR.MUI.MED.REC.1401.267.

Financial support and sponsorship

This study was financially supported by the Vice Chancellor for Research and Technology, Isfahan University of Medical Sciences. Publication fee will be charged according to the journal instructions to authors.

Conflicts of interest

There are no conflicts of interest.

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