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REVIEW ARTICLE

Neonatal hyperbilirubinemia and repercussions on neurodevelopment: A systematic review

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Abstract

Background: Accumulation of bilirubin above normal levels is considered a neurological risk factor for both premature and full-term newborns. This systematic review aimed to determine the effect of neonatal hyperbilirubinemia on neurodevelopment in preterm and full-term newborns.

Methods: PubMed, EMBASE, Cochrane Library, CINAHL, PsycINFO, Scopus and Lilacs databases were searched for articles published until 1 June 2022. The quality of cohort and case–control studies was assessed with the Newcastle–Ottawa Scale, and the MINCir scale was used to evaluate the methodological quality of therapy studies or the therapeutic procedures. Premature neonates without neurological conditions and those born at term with hyperbilirubinemia as the sole risk factor were included. Studies reporting one or more neurodevelopmental outcomes were included with an inter-group comparison of a hyperbilirubinemia group versus a non-hyperbilirubinemia or non-pathological hyperbilirubinemia group. The main outcomes were auditory function, visual function, cognitive function, motor function, behavior, global development and neurological risk.

Results: The search identified 951 studies, 19 of which ($n = 2210$ newborns) were finally included. Fifteen of the cohort and case–control studies presented low risk of bias, and six studies showed high methodological quality. Within the preterm population, hyperbilirubinemia as the sole risk factor was not shown to affect neurodevelopment. Auditory, neurological and motor development alterations were found in the population of full-term newborns with hyperbilirubinemia, which were more evident during the first year of life.

Conclusions: Elevated bilirubin levels may be a trigger for the onset of neurodevelopmental disorders in full-term infants during the first year of life. More studies are warranted in the preterm population with hyperbilirubinemia to draw conclusions about its impact on their neurodevelopment.

KEYWORDS
neonatal hyperbilirubinemia, neonatal jaundice, neurodevelopment, neurological development, pediatrics

1 | INTRODUCTION

Key messages

- Hyperbilirubinemia is one of the non-neurological risk factors that we find in the population of newborns, which can cause alterations in neurodevelopment
- Elevated bilirubin levels can trigger the appearance of neurodevelopmental disorders in full-term newborns during the first year of life (auditory, neurological and motor development alterations)
- Newborns with non-neurological risk factors should follow an early detection and early intervention program to improve their neurodevelopment

The accumulation of bilirubin, known as hyperbilirubinemia, produces jaundice, a clinical sign in which the skin of the newborn acquires a yellowish color. Bilirubin is a yellow pigment that is naturally found in the human body during the recycling process of aging red blood cells (Kumar, 1999). About 50% of full-term infants and 80% of premature infants develop this condition in their first week of life (Kumar, 1999), making it one of the most common reasons for readmission to the hospital after discharge (Gale et al., 2001). High levels of bilirubin can cross the blood–brain barrier, be deposited in the brain and cause the development of kernicterus. This condition is the chronic form of bilirubin encephalopathy and can further cause athetoid cerebral palsy, hearing loss and failure of upward gaze (Turkel et al., 1980). The exact level of bilirubin that is neurotoxic is unclear, and it is not known what bilirubin levels are related to each neurodevelopmental disorder.

Unconjugated or free bilirubin is measured to detect hyperbilirubinemia in newborns (Okwundu et al., 2012) and, although it can be beneficial as an antioxidant, high doses become neurotoxic (Jenabi et al., 2020; Rose & Vassar, 2015). Bilirubin levels in the blood of 5–7 mg/dL are considered normal and higher levels result in the appearance of a yellow color in the skin of newborns. Five percent of neonates have blood bilirubin levels of 17 mg/dL, and only 1.2% of these reach 20 mg/dL, with levels of this pigment above this figure being considered high; >25 mg/dL, very high; and >30 mg/dL, extreme (Bhutani et al., 1999). Accumulation of bilirubin above normal levels is considered a neurological risk factor for both premature and full-term newborns, as are other factors such as premature birth, birth weight, intrauterine growth retardation, perinatal asphyxia, sepsis, bronchopulmonary dysplasia, neonatal hypoglycemia, periventricular leukomalacia and intraventricular hemorrhage (Milner et al., 2017; Tian et al., 2018).

Additionally, bilirubin levels have been shown to augment the presence of other risk factors such as low birth weight or low gestational age (Okwundu et al., 2012; Rose & Vassar, 2015), which can increase the risk of neurological damage in the premature population. Unconjugated or free bilirubin can travel in the blood into the basal ganglia (Turkel et al., 1980; Volpe, 2001), hippocampus (Volpe, 2001) and cerebellum (Volpe, 2001), causing two neurological conditions when it reaches extreme levels: acute bilirubin encephalopathy (Greco et al., 2016) and its chronic version, kernicterus (Turkel et al., 1980; Volpe, 2001), which can result in choreoathetoid cerebral palsy (Turkel et al., 1980; Volpe, 2001), the most severe of the conditions produced by abnormal concentrations of this pigment (Turkel et al., 1980). Furthermore, the chronic state of neurotoxic bilirubin levels can produce minor neurological alterations, including auditory dysfunctions associated with language disorders (Amin et al., 2019; Brown et al., 1985; Rose & Vassar, 2015; Vohr et al., 1990; Wusthoff & Loe, 2015), decreased intellectual function associated with alterations in executive functions (Amin et al., 2019; Ross, 2003; Wusthoff & Loe, 2015), visual impairment (Amin et al., 2019; Brown et al., 1985; Paludetto et al., 2002; Rose & Vassar, 2015) and dental abnormalities (Rose & Vassar, 2015; Turkel et al., 1980; Volpe, 2001). Not only the neurological damage that high doses produce in the nervous system has been evidenced (Okwundu et al., 2012), but moderate doses have been recently associated with minor neurological dysfunctions in full-term children at 1 year of life (Soorani-Lunsing et al., 2001), as well as the possibility of developing certain pathologies that affect neurodevelopment, such as autism spectrum disorder (ASD) (Amin et al., 2011; Jenabi et al., 2020) or attention-deficit hyperactivity disorder (ADHD) (Wusthoff & Loe, 2015). Minor neurological dysfunction (MND) is a condition detected by a standardised neurological examination that is age-specific and examines a number of dysfunctional neurological domains, such as posture and tone, coordination and fine manipulative ability. There are two types of MND: simple MND, which refers to typical but non-optimal brain function with deviations in a limited number of domains and has limited clinical relevance, and complex MND, which is clinically relevant with non-optimal brain functions in several domains (De Roubaix et al., 2021).

The Perinatal Risk Inventory (Schemer & Sexton, 1991) is an assessment tool that serves to determine the level of neurological risk in premature and full-term neonates based on the risk factors they present, among which is hyperbilirubinemia. The Nursery Neurobiologic Risk Score (Brazy et al., 1991) is another instrument that includes hyperbilirubinemia as a neurological risk factor depending on the weight of the newborn. Their use through the exploration of the medical history can be a good complement to other early detection tools with greater scientific evidence, such as the General Movements Assessment or the Hammersmith Neonatal Neurological Examination, which will allow the identification of high-risk newborns (Hadders-Algra, 2021; Novak et al., 2017).

Perinatal care, such as blood transfusion and phototherapy (Okwundu et al., 2012), has contributed to the resolution of jaundice and extreme hyperbilirubinemia. It has also significantly decreased the incidence of kernicterus, especially in countries where these treatments are adequately applied, although monitoring the relevant

symptomatology is still recommended to avoid an increase in cases (Badawi et al., 2021) as delaying the phototherapy treatment may lead to the development of this brain dysfunction (Rose & Vassar, 2015). Overall, perinatal care (Badawi et al., 2021), early evaluation (Badawi et al., 2021) and early intervention (Badawi et al., 2021) have been shown to reduce neurological damage (Wu et al., 2020) and minimise the relevant sequelae.

Physiotherapists are among the professionals who work at an early stage, both in neonatal intensive care units and in early care programs (Nwabara et al., 2017), in this population at high risk of suffering neurodevelopment disorders where motor and other development aspects may be affected and the consequences of non-extreme levels of hyperbilirubinemia are not yet well known (Rose & Vassar, 2015). Early interventions at the age of 0–2 years are the optimal therapeutic window to achieve neuroplastic changes (Morgan et al., 2021). Therefore, knowing the possible neurological sequelae in newborns with hyperbilirubinemia is imperative to detect potential neurodevelopmental disorders early on and be able to improve the functionality of these children with the available therapeutic tools (Byrne & Garber, 2013; Mahoney & Cohen, 2005).

The aim of this systematic review was to assess the effect of neonatal hyperbilirubinemia above 15 mg/dL on the different aspects of neurodevelopment (motor area, cognitive area and sensory area) in preterm and full-term newborns, as well as to report on the evolution of these patients.

2 | METHODS

This systematic review has been conducted following the PRISMA recommendations (Moher et al., 2009) for the development of systematic reviews and meta-analysis, based on the formulation of the PICO question (population/patients, intervention, comparison and outcome) 'What is the effect of neonatal hyperbilirubinemia on neurodevelopment in preterm and full-term newborns?' It has been registered in the PROSPERO database (registration ID: CRD42021233332).

2.1 | Search strategy

Articles were searched in PubMed, EMBASE, Cochrane Library, CINAHL, PsycINFO, Scopus and Lilacs databases. The search was restricted to studies involving humans and there was no limit on the year of publication. A cross-search was also performed of the references cited in the articles found and the references of the eligible articles were examined to complete the systematic literature search. Table A1 displays the search strategies for the different databases. The search was last updated on 1 June 2022. Two authors conducted the electronic search and the initial title and abstract screening and two other authors reviewed the records identified for full-text screening. The screening and eligibility assessments were performed using RAYYAN QCRI (https://rayyan.qcri.org/).

2.2 | Eligibility criteria

The inclusion criteria were as follows: (1) cohort studies and case–control studies, (2) including children born prematurely without neurological conditions and/or born at term with hyperbilirubinemia as the sole risk factor and (3) studies reporting one or more neurodevelopmental outcomes and including a comparison between a hyperbilirubinemia group and a non-hyperbilirubinemia or non-pathological hyperbilirubinemia group.

The exclusion criteria were as follows: (1) studies that included infants who developed hyperbilirubinemia after the neonatal period, (2) including subjects who presented one or more neurological risk factors (seizures, intraventricular hemorrhage, periventricular leukomalacia or hydrocephalus) or (3) the following types of publication: case series, conference abstracts, randomised clinical trials, systematic reviews and meta-analyses.

2.3 | Data extraction, risk of bias assessment and methodological quality assessment

A table was created ad hoc to summarise the following information from the original reports: (1) author, country and year of publication; (2) study type; (3) sample characteristics (study population and sample size); (4) level of bilirubin; (5) treatments; (6) neurodevelopmental test; (7) neurodevelopmental disorder; and (8) follow-up. The methodological quality assessment was completed using the Newcastle–Ottawa Scale (NOS) for cohort and case–control studies (Wells et al., 2013) and with the MINCir scale (Cartes-velásquez et al., 2014) for therapy studies. The quality of evidence was also evaluated based on the classification by the Oxford's Centre for Evidence-Based Medicine (CEBM) (OCEBM Levels of Evidence Working Group, 2011). Disagreements in any of the above-mentioned assessments were resolved by consensus or consulting with a third author if necessary. The literature search, data extraction, risk of bias assessment and quality assessment were conducted by two independent reviewers and a third reviewer intervened when inconsistencies remained after discussion.

3 | RESULTS

3.1 | Literature search

The initial search of the different databases identified 891 articles, and 60 more articles were identified through the review of the cited bibliographic references, yielding a total of 951 eligible articles. Following the removal of duplicates, 936 articles were screened of which 822 were finally excluded for not being relevant to the present review. The full text of 110 articles was evaluated, and 93 of them were excluded for the following reasons: (1) full-term newborns with another risk factor ($n = 1$), (2) premature newborns with any risk factor associated with neurological disorders ($n = 5$), (3) absence of a

control group without hyperbilirubinemia ($n = 73$), (4) not reporting neurodevelopment outcomes ($n = 6$), (5) type of publication other than those accepted in the inclusion criteria ($n = 1$), (6) not reporting data from the control group ($n = 1$) and (7) not discriminating between full- and preterm subjects ($n = 6$) (Table A2). In addition, two articles identified from the manual search were selected. Finally, the present systematic review examined a sample of 19 studies (Figure 1).

3.2 | Risk of bias and methodological quality

Table A3 shows the risk of bias of the included case–control and cohort studies measured with the NOS, with scores between 5 and 9 points for cohort studies (maximum score of 9). The quality was good in 94.73% of cases in terms of the selection of participants, in 68.42% in terms of comparability and in 75.43% in terms of outcomes or exposure. Table A4 displays the methodological quality of therapy (or therapeutic procedures) studies measured with the MINCir. The quality was good only in 31.57% of cases with an inter-rater agreement of 72.47%.

3.3 | Systematic review

Eighteen studies (Agrawal et al., 1998; Bengtsson & Verneholt, 1974; Besli et al., 2020; Y. Chen & Kang, 1995; de Almeida et al., 2002; Deorari et al., 1994; Grimmer et al., 1999; Gupta et al., 1990; Hokkanen et al., 2014; Holmes et al., 1968; Hung, 1989; Kahraman et al., 2021; Lunsing et al., 2013; Özmert et al., 1996; Rubin et al., 1979; Sabatino et al., 1996; Soorani-Lunsing et al., 2001; Wong et al., 2006) analysed the effect of neonatal hyperbilirubinemia in full-term newborns and one study (Can et al., 2015) in preterm infants. An overall sample of 2210 subjects was evaluated of which 2023 were born at term and 187 were premature. The average gestational age of neonates born at term with elevated levels of bilirubin was 38.2–40.4 weeks, 40.70% were girls and the birth weight was 2630–3505 g, whereas in the control group without hyperbilirubinemia, the average gestational age was 38.2–40.8 weeks, 48.78% were girls and the birth weight was 2600–3616 g. In the case of premature infants, the average gestational age was 35.2 weeks, 30.58% were girls, and the average weight at birth was 2876 g for those with high levels of bilirubin, whereas in the control group, the average gestational age was 35.5 weeks and the birth weight was 2916 g (gender distribution not reported) (Table A5).

The delivered treatments to reduce hyperbilirubinemia were phototherapy (Agrawal et al., 1998; Can et al., 2015; Y. Chen & Kang, 1995; Deorari et al., 1994; Grimmer et al., 1999; Hokkanen et al., 2014; Hung, 1989; Kahraman et al., 2021; Lunsing et al., 2013; Sabatino et al., 1996; Soorani-Lunsing et al., 2001; Wong et al., 2006) ($n = 12$) and blood transfusion ($n = 14$) (Agrawal et al., 1998; Bengtsson & Verneholt, 1974; Y. Chen & Kang, 1995; Deorari et al., 1994; Grimmer et al., 1999; Gupta et al., 1990; Hokkanen et al., 2014; Holmes et al., 1968; Hung, 1989; Kahraman et al., 2021; Özmert et al., 1996; Rubin et al., 1979; Sabatino et al., 1996; Wong

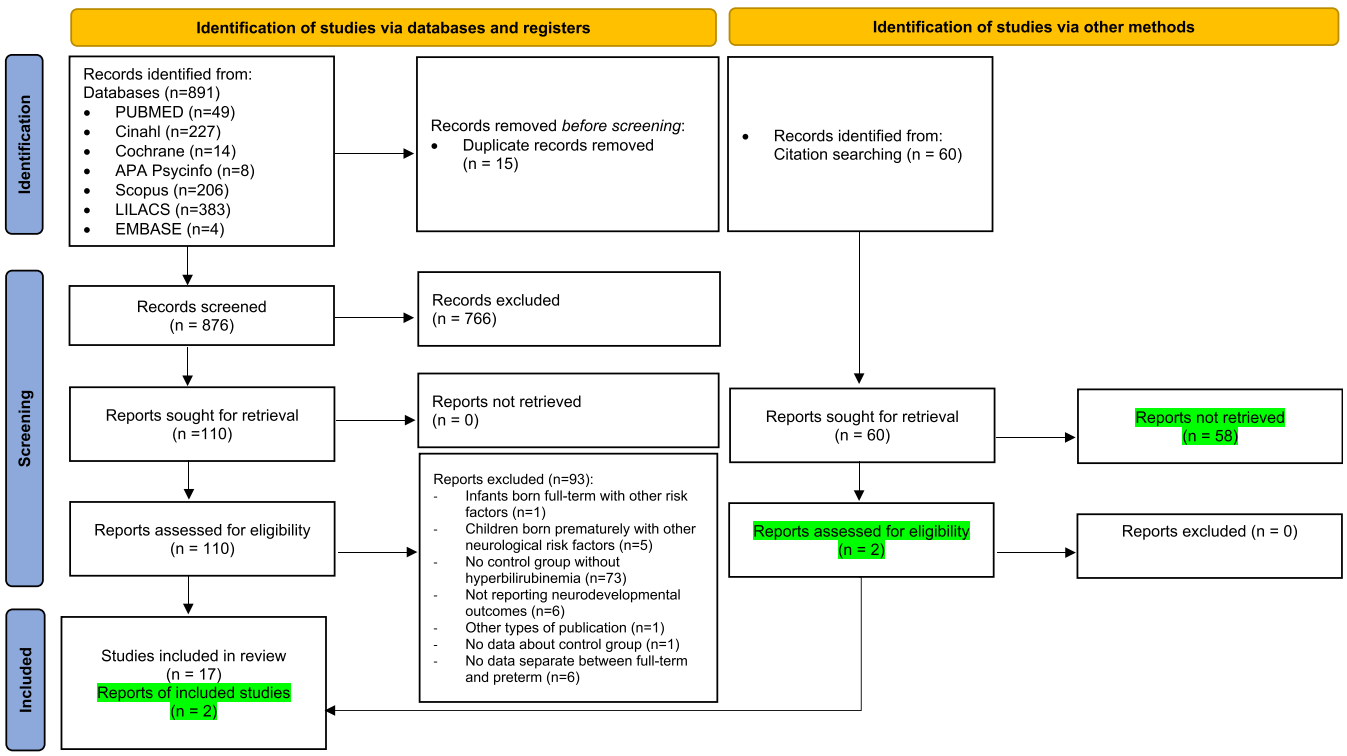

FIGURE 1 Flowchart of the study selection process.

et al., 2006), which are the two interventions recommended by clinical practice guidelines for the resolution of pathologically increased bilirubin (Table A6).

Different tools were used to measure neurodevelopment, evaluating both the overall development and specific areas of child development (Table A7).

The vast majority of the analysed studies included a sensory evaluation. Twelve of the studies assessed audition, eight of which reported hearing loss compared to the control group (Agrawal et al., 1998; Bengtsson & Verneholt, 1974; Besli et al., 2020; de Almeida et al., 2002; Gupta et al., 1990; Hung, 1989; Özmert et al., 1996; Sabatino et al., 1996). The most commonly used tool was the auditory brainstem response (Agrawal et al., 1998; Besli et al., 2020; Can et al., 2015; de Almeida et al., 2002; Deorari et al., 1994; Gupta et al., 1990; Hung, 1989; Özmert et al., 1996; Sabatino et al., 1996; Wong et al., 2006), followed by audiometry (Deorari et al., 1994; Holmes et al., 1968), hearing test (Bengtsson & Verneholt, 1974) and oto-emissions (Can et al., 2015; de Almeida et al., 2002). Visual assessments were also performed as part of the sensory evaluations via visual evoked potentials (Y. Chen & Kang, 1995; Özmert et al., 1996) or visual examination (Wong et al., 2006), with only one of the authors reporting differences between the hyperbilirubinemia and the control groups, specifically an affectation of gross and fine motor skills due to an alteration in the response of the visual sensory pathway (Y. Chen & Kang, 1995).

In terms of motor evaluation, an area without a gold standard measurement instrument, three studies were found that assessed gross motor skills using different tools, such as the modified Oseretsky test of motor proficiency (Holmes et al., 1968), Test of Motor Impairment (Hokkanen et al., 2014) and a global evaluation of gross motricity (Bengtsson & Verneholt, 1974). Only one (Bengtsson & Verneholt, 1974) of the studies included in this review assessed fine motor skills within a global development evaluation. All articles evaluating the gross motor function showed altered outcomes in the group of infants with high bilirubin compared to the control group. These alterations were highly variable, going from worse coordination, balance and speed of movement execution (Holmes et al., 1968) to the most severe motor limitations of choreoathetoid cerebral palsy (Bengtsson & Verneholt, 1974). Within fine motor disorders, worse unimanual and bimanual functioning has been observed (Hokkanen et al., 2014; Holmes et al., 1968).

A cognitive/behavioral assessment was another developmental area evaluated in the different studies. Cognitive aspects were assessed in a total of four studies, with a preferential use of the Wechsler Intelligence Scale for Children (Hokkanen et al., 2014; Özmert et al., 1996; Rubin et al., 1979), followed by the Illinois Test of Psycholinguistic Abilities (Hokkanen et al., 2014; Rubin et al., 1979) or other tests such as the Metropolitan Readiness Tests (Rubin et al., 1979), Stanford–Binet Scale (Rubin et al., 1979), Terman–Merrill test (Bengtsson & Verneholt, 1974), WIT Test (Bengtsson & Verneholt, 1974) and Reading and Spelling Test (Hokkanen et al., 2014). Behavioral aspects were evaluated via the Toddler Behavior Assessment Questionnaire in one study (Lunsing et al., 2013) and with a questionnaire for parents in another study (Soorani-Lunsing et al., 2001). Only one of the studies evaluating cognitive aspects found altered outcomes for this neurodevelopment area in the group of children affected by hyperbilirubinemia, where the subjects who had suffered hyperbilirubinemia obtained lower academic grades compared to the control group (Hokkanen et al., 2014).

In addition to evaluating the different areas of development, six studies assessed the global development of children, mainly using the Denver Developmental Screening Test (Agrawal et al., 1998; Besli et al., 2020; Y. Chen & Kang, 1995) but also with other tools, such as the Brunet–Lezine scale (Sabatino et al., 1996), the development quotient (Deorari et al., 1994) and the Bayley Mental and Motor Scales of Infant Development (Rubin et al., 1979). Only one study reported alterations in global development, specifically lower scores in the Denver Developmental Screening Test when comparing it with children with normal bilirubin levels (Agrawal et al., 1998).

Finally, this review observed a large number of studies including a neurological evaluation. Specifically, nine studies assessed neurological function, with the most frequently used tool being the general neurological evaluation (Bengtsson & Verneholt, 1974; Besli et al., 2020; Özmert et al., 1996; Rubin et al., 1979; Wong et al., 2006), followed by the APGAR score (Gupta et al., 1990; Hokkanen et al., 2014; Lunsing et al., 2013; Rubin et al., 1979) and Prechtl's General movement assessment (Lunsing et al., 2013; Soorani-Lunsing et al., 2001), although other tests were also employed, including the Touwen's infant neurological examination (Grimmer et al., 1999), Hempel's neurologic examination (Lunsing et al., 2013), screening method of Amiel–Tison (Soorani-Lunsing et al., 2001) and Michelsson's Neurodevelopmental screening examinations (Hokkanen et al., 2014). Of note, four studies assessed the neurological risk in newborns via general movements evaluation (Kahraman et al., 2021; Lunsing et al., 2013; Soorani-Lunsing et al., 2001) or clinical risk index of babies for determining the mortality risk. Finally, four studies conducted a general physical evaluation (Bengtsson & Verneholt, 1974; Holmes et al., 1968; Özmert et al., 1996; Wong et al., 2006) as a complementary tool to those described above. In summary, eight studies found neurological alterations, among which the main pathologies were as follows: choreoathetoid cerebral palsy, diagnosed with early detection tools or clinical signs before the age of 2 years (Bengtsson & Verneholt, 1974; Besli et al., 2020; Kahraman et al., 2021; Özmert et al., 1996); ADHD, diagnosed through a retrospective study where subjects were questioned at the age of 30 years (Hokkanen et al., 2014); and MND, diagnosed by clinical signs and neurological evaluations at the age of 1 year (Grimmer et al., 1999; Lunsing et al., 2013; Özmert et al., 1996; Soorani-Lunsing et al., 2001). Moreover, all of these studies reported neurological disorders during the first year of life, such as alterations in muscle tone (hypotonia).

All these evaluations were performed at different time points to be able to confirm or reject the studied alterations. A significant number of the included studies conducted an early follow-up within the

two first years of life, whereas follow-up periods between 2 and 6 years of age or even beyond 6 years were more infrequent.

4 | DISCUSSION

The present review aimed to analyse the effect of elevated bilirubin levels on neurodevelopment in both preterm and full-term infants.

Our findings in the premature population showed that hyperbilirubinemia as the sole risk factor did not entail potential consequences for the neurodevelopment of these children. However, the limited number of studies (only one study (Can et al., 2015) with low risk of bias and good methodological quality) does not allow extrapolation of these outcomes, since hyperbilirubinemia is frequently accompanied by other risk factors in this population, mainly low birth weight, that enhance the negative impact on neurodevelopment. Therefore, the more risk factors are present in these infants, the more continued surveillance is necessary.

Different studies reflect that this population could present neurological alterations around 17% (Newman et al., 2006) such as tone alterations (Brites & Fernandes, 2015; Lunsing, 2014), in addition to motor alterations such as coordination problems (Brites & Fernandes, 2015; Lunsing, 2014) and gait disturbances (Lunsing, 2014).

On the contrary, the current evidence does not clearly reflect that this population group may present sensory alterations, since the results obtained in the different studies are contradictory (Brites & Fernandes, 2015; Can et al., 2015). The same happens with the possible development of neurodevelopmental disorders such as ASD, epilepsy, cerebral palsy or behavioral disorders (Brites & Fernandes, 2015; Olusanya et al., 2018; Wusthoff & Loe, 2015).

Current hypotheses about the underlying mechanisms causing dysfunctions in different developmental areas in premature newborns point to alterations in the processes of myelination, neurogenesis and gliogenesis in an immature brain that, in combination with the toxic capacity of the pigment, lead to an inflammatory response (cytokine cascade) that aggravates the physiological development of these processes, as referred by Brites and Fernandes (2015). Moreover, additional risk factors frequently presented in the premature population, such as low birth weight, hypoxia or sepsis, help the pigment that is not bound to albumin to cross the blood–brain barrier, so the combination of such factors with high bilirubin leads to a worsening of the clinical picture of the newborn (Brites & Fernandes, 2015).

Rose and Vassar (2015) also stated that the time of onset of the toxic reaction produced by elevated bilirubin levels makes a great difference in the long-term prognosis of these patients, even leading to hearing impairment in premature children or the development of cerebral palsy in infants born at term. Therefore, it is necessary to monitor this premature population and pay more attention to more risk factors they suffer (Hansen, 2011).

Bilirubin above normal physiological parameters in infants born at term resulted in alterations in auditory development [nine (Agrawal et al., 1998; Bengtsson & Verneholt, 1974; Besli et al., 2020; Y. Chen & Kang, 1995; Grimmer et al., 1999; Gupta et al., 1990; Hung, 1989; Kahraman et al., 2021; Wong et al., 2006) of the 11 analysed studies presented low risk of bias, and eight (Agrawal et al., 1998; Besli et al., 2020; Y. Chen & Kang, 1995; Deorari et al., 1994; Grimmer et al., 1999; Gupta et al., 1990; Hung, 1989; Sabatino et al., 1996) showed low methodological quality], neurological development [of the 10 examined studies (Bengtsson & Verneholt, 1974; Besli et al., 2020; Grimmer et al., 1999; Gupta et al., 1990; Hokkanen et al., 2014; Lunsing et al., 2013; Özmert et al., 1996; Rubin et al., 1979; Soorani-Lunsing et al., 2001; Wong et al., 2006), all presented low risk of bias and six were classified with low methodological quality (Besli et al., 2020; Grimmer et al., 1999; Gupta et al., 1990; Lunsing et al., 2013; Özmert et al., 1996; Soorani-Lunsing et al., 2001)] and motor development [two (Bengtsson & Verneholt, 1974; Hokkanen et al., 2014) of three studies showed low risk of bias and good methodological quality].

Ross (2003) concluded that moderately elevated levels of bilirubin also affect sensory development in full-term infants. W. Chen et al. (2023) recently found that auditory sensory disturbances in the full-term population, caused by high levels of bilirubin, can be resolved after 1 year of life with nutritional neuro-drugs. In addition, these authors referred that the level of pigment in each subject will determine the magnitude of hearing damage and their subsequent recovery.

Gordon et al. (2005) compared full-term infants with elevated bilirubin levels with subjects who had suffered sepsis during their neonatal period and reported that the neurologic abnormalities observed in the former group were more severe than those developed after sepsis and that these sequelae usually appear at the age of 18–32 months. Sgro et al. (2011) also found a high percentage of children with hypotonia (22/32) within a group of infants with high bilirubin levels in the neonatal period. These authors concluded that the earlier hyperbilirubinemia appears, the earlier acute bilirubin encephalopathy develops, with the subsequent neurological effects at such an early age, hence the need for long-term follow-up of neurodevelopment.

In terms of global development, four (Agrawal et al., 1998; Besli et al., 2020; Y. Y. Chen & Kang, 1995; Rubin et al., 1979) of the six examined studies presented low risk of bias and five (Agrawal et al., 1998; Besli et al., 2020; Y. Chen & Kang, 1995; Deorari et al., 1994; Sabatino et al., 1996) had low methodological quality. The most prevalent pathologies were choreoathetoid cerebral palsy, ADHD and MND, which were more evident during the first year of life. Jenabi et al. (2020) also suggested that jaundice in the full-term population could be a risk factor for developing ASD.

Ross (2003) reported alterations in motor control in full-term children with moderately elevated bilirubin levels. Similarly, Dubey et al. (2021) observed that 5.5% of full-term infants with high bilirubin levels presented motor abnormalities, as detected at 1 year of life with the Development Assessment Scale for Indian Infants (a revised version of the Bayley Scale of Infant Development). Gordon et al. (2005) also reported difficulty in maintaining a seating or standing position, movement disorders and eye-movement disorders (43%, 48% and 56% of the subjects, respectively) in a group of full-term

infants with high bilirubin levels. All the investigations correlated these results with bilirubin levels in the neonatal period.

In other terms as the cognitive and behavioral aspects, this review found that hyperbilirubinemia can affect attention in full-term infants (all six included studies (Bengtsson & Verneholt, 1974; Hokkanen et al., 2014; Lunsing et al., 2013; Özmert et al., 1996; Rubin et al., 1979; Soorani-Lunsing et al., 2001) showed low risk of bias and three of them (Bengtsson & Verneholt, 1974; Hokkanen et al., 2014; Rubin et al., 1979) presented good methodological quality). However, the study by Ross (2003) questioned the potential effect on cognitive development, similar to Wusthoff et al. (2015) who did not find evidence for cognitive impairment associated with a lower intelligence quotient despite reporting dysfunctions in executive functions. On the contrary, Amin et al. (2019) pointed out that the potential effect on cognition in the population of full-term newborns could be related to being male.

The impact of bilirubin on neurodevelopment remains unclear with the currently available scientific evidence and studies indicating the need for further research on this risk factor in both the preterm and full-term population. Okwundu et al. (2012) evaluated the effect of phototherapy in premature or low-birth-weight infants and stated the need for further research. Wusthoff and Loe (2015) highlighted the need for more studies about the effect of bilirubin in the population born at term and the impact on developing certain pathologies, such as ADHD or ASD given the contradictory outcomes of the current evidence. A recent study comparing the full-term and premature populations pointed out milk supplementation, typically administered to premature infants, as a potential differentiating factor that could play a protective role in some cases, as exclusive breastfeeding has been shown to be the main cause of jaundice in the full-term population (Wilde, 2022). Another study even reported that the difference in neurodevelopmental damage between population groups depends on age, the pigment concentration level, the age at which hyperbilirubinemia appears and the brain location where the pigment is deposited (Zhang et al., 2023).

Currently, different clinical trials are being conducted to study potential modifications in the production of bilirubin to avoid its toxic effect on the nervous system. The research includes animal models, such as the administration of different drugs to Gunn rats that could reverse the hyperbilirubinemia levels. And even, with this animal model, it is being studied within the preterm population, since it is a population group where very little has been studied about this health condition. Studies using animal and in-vitro models have also been performed by administering metalloporphyrins to reduce the creation of bilirubin, which would reduce neurological damage produced by the accumulation of bilirubin. However, its prophylactic or therapeutic application is being questioned until determining the safety of such intervention.

Therefore, specific evaluations adjusted to the age of these subjects are warranted to quantify potential neurodevelopmental alterations (Lunsing, 2014). Since the effects on neurodevelopment are detected during the first 2 years of life and rarely beyond this age, such follow-ups must be conducted systematically, starting at the neonatal intensive care unit with its detection and continuing during their handover to early care for prompt intervention. The General Movements Assessment appeared to be an adequate tool for the evaluation and follow-up of these high-risk subjects during the first 5 months of life [the three included studies (Kahraman et al., 2021; Lunsing et al., 2013; Soorani-Lunsing et al., 2001) presented low risk of bias and two (Lunsing et al., 2013; Soorani-Lunsing et al., 2001) of them showed low methodological quality]. In sight of the findings of Soorani-Lunsing et al. (2001), a review by Lunsing (2014) reported that this tool was effective in predicting any MND in 70% of children. In addition, other instruments should be employed for the assessment of neurological function and global development, including motor function. Such tools must be backed by the strongest scientific evidence available in order to perform an optimal screening of infants at high neurological risk with elevated bilirubin levels. Finally, these evaluation methods should be complemented with other scales that measure different risk factors, such as the Perinatal Risk Inventory or the Nursery Neurobiologic Risk Score, since a correlation has been shown between these tools and the General Movements Assessment (de Vries & Bos, 2010).

Novak et al. (2017) reported that the vast majority of studies that sought the early detection of cerebral palsy referred to risk factors such as prematurity or encephalopathy, since these pathologies are rapidly detected. However, there is little evidence on the factors related to the 50% of cerebral palsy that is diagnosed at a later time after an uncomplicated birth (Novak et al., 2017). On the other hand, Lee et al. (2021) also stated that the presence of certain risk factors, such as hyperbilirubinemia, hypoglycemia, cranial deformities or intrauterine growth retardation, may increase the risk of developing ASD in the medium-to-long term (Lee et al., 2021). This poses a challenge for professionals involved in early care, who are required to use the best available tools for the early detection and follow-up of subjects at high neurological risk who present any risk factors potentially leading to the development of a neurodevelopmental disorder in the short, medium and long terms (Te Velde et al., 2019).

4.1 | Strengths and limitations

This review showed that newborns can develop various dysfunctions in different developmental areas even if hyperbilirubinemia is a clinically controlled risk factor in developed countries, which prevents the most severe form of neurodevelopment alterations (kernicterus). This research found more studies in the term population, which appears to indicate that these neurodevelopmental sequelae are more evident in the full-term population, probably due to the greater development of the nervous system compared to the preterm population. However, the latter subjects show greater complexity when hyperbilirubinemia is present as the sole risk factor so further research is warranted in this area.

Among the limitations of this study was the difficulty in finding clinical studies in the preterm population with high bilirubin levels and low gestational age as the sole risk factors since premature infants

usually present a greater number of risk factors than full-term newborns. Another limitation is that the vast majority of studies focused on the neurodevelopmental consequences at an early age, with limited studies examining effects in the medium and long term. Of note, several studies did not provide all the necessary information to draw a more accurate analysis, presenting a significant limitation. In addition, the studies included in this review were not randomised clinical studies, thus lowering the level of evidence. Finally, there are very few studies that analysed the different degrees of hyperbilirubinemia and its possible consequences, which raises the possibility for a future line of research.

4.2 | Recommendations for clinical practice

The different clinicians working with both preterm and full-term newborns must monitor infants with hyperbilirubinemia at birth, as there are various neurodevelopmental consequences that could affect them in the short, medium and long terms, hindering their learning and participation in the different natural environments. Moreover, a close follow-up of the premature population is necessary and must be intensified in the presence of increased numbers of risk factors, as they appear to have a multiplying effect and therefore entail more severe neurodevelopmental consequences and lead to the occurrence of different disorders. Finally, optimal therapeutic tools are necessary for clinicians to intervene in order to lower bilirubin concentrations, thus avoiding further exposure and a greater toxic effect on the central nervous system.

5 | CONCLUSIONS

Bilirubin levels above the normal physiological parameters in full-term neonates can trigger the onset of neurodevelopmental disorders, despite the interventions recommended by clinical practice guidelines, mainly phototherapy and blood transfusion. Very high or extreme bilirubin levels can cause kernicterus (choreoathetoid cerebral palsy), whereas moderate bilirubin levels may cause hearing impairment, motor disturbances and minor neurological disturbances. Given the current level of evidence, more conclusive studies in the preterm and full-term populations are warranted to assess the repercussions of hyperbilirubinemia including cognitive and visual alterations and the possible development of ADHD or ASD.

The more risk factors are present in a newborn, the higher the likelihood of suffering neurodevelopmental alterations in the short, medium and long terms. Therefore, periodic follow-ups of preterm or early-term newborns with high bilirubin levels conducted by specialised care teams are necessary in order to perform interventions to improve neurodevelopment.

AUTHOR CONTRIBUTIONS

Javier Merino-Andrés: Conceptualisation; Methodology; Investigation; Writing e original draft. **Soraya Pérez-Nombela:** Conceptualisation; Writing; review and editing; Supervision. **Celia Álvarez-Bueno:** Formal analysis; Writing and editing. **Álvaro Hidalgo-Robles:** Conceptualisation; Methodology. **Irene Ruiz-Becerro:** Formal analysis and review. **Francisco Javier Fernández-Rego:** Conceptualisation; Writing; review and editing; Supervision. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CLINICAL TRIAL REGISTRATION

PROSPERO database (registration ID: CRD42021233332).

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APPENDIX A

TABLE A1 Search strategy for the different databases.

Database	Search strategy
Pubmed	('infant'[mesh] OR 'premature birth'[mesh] OR 'pediatrics'[mesh] OR 'infant, newborn'[mesh]) AND ('hyperbilirubinemia, neonatal'[mesh] OR 'hyperbilirubinemia'[mesh] OR 'jaundice, neonatal'[mesh]) AND ('neurodevelopment' OR 'neurodevelopmental disorders' OR 'neurological sequelae')
EMBASE	('infant' OR 'preterm' OR 'pediatric' OR 'newborn') AND ('neonatal hyperbilirubinemia' OR 'hyperbilirubinemia' OR 'jaundice') AND ('neurodevelopment' OR 'neurodevelopmental disorders' OR 'neurological sequelae')
Cochrane library	('infant' OR 'preterm' OR 'pediatric' OR 'newborn') AND ('neonatal hyperbilirubinemia' OR 'hyperbilirubinemia' OR 'jaundice') AND ('neurodevelopment' OR 'neurodevelopmental disorders' OR 'neurological sequelae')
CINAHL	('infant' OR 'preterm' OR 'pediatric' OR 'newborn') AND ('neonatal hyperbilirubinemia' OR 'hyperbilirubinemia' OR 'jaundice') AND ('neurodevelopment' OR 'neurodevelopmental disorders' OR 'neurological sequelae')
PsycINFO	('infant' OR 'preterm' OR 'pediatric' OR 'newborn') AND ('neonatal hyperbilirubinemia' OR 'hyperbilirubinemia' OR 'jaundice') AND ('neurodevelopment' OR 'neurodevelopmental disorders' OR 'neurological sequelae')
SCOPUS	('infant' OR 'preterm' OR 'pediatric' OR 'newborn') AND ('neonatal hyperbilirubinemia' OR 'hyperbilirubinemia' OR 'jaundice') AND ('neurodevelopment' OR 'neurodevelopmental disorders' OR 'neurological sequelae')
LILACS	('infant' OR 'preterm' OR 'pediatric' OR 'newborn') AND ('neonatal hyperbilirubinemia' OR 'hyperbilirubinemia' OR 'jaundice') AND ('neurodevelopment' OR 'neurodevelopmental disorders' OR 'neurological sequelae')

TABLE A2 List of excluded full-text articles and primary reason for exclusion.

#	Study	Title
Infants born at full-term with other risk factors ($n = 1$)		
	Scheidt PC et al. 1991	Intelligence at 6 years in relation to neonatal bilirubin levels: Follow-up of the National Institute of Child Health and Human Development clinical trial of phototherapy
Children born prematurely with other risk factors (neurologic disorder, low weight at birth, etc.) ($n = 5$)		
	Chsin R et al. 1979	Cochlear and brain stem responses in hearing loss following neonatal hyperbilirubinemia
	Gartner LM et al. 1970	Kernicterus: High incidence in premature infants with low serum bilirubin concentrations
	Graziani LJ et al. 1992	Neurodevelopment of preterm infants: Neonatal neurosonographic and serum bilirubin studies
	Van de Bor M et al. 1992	Hyperbilirubinemia in low birth weight infants and outcome at 5 years of age.
	Yeo KL et al. 1998	Outcomes of extremely premature infants related to their peak serum bilirubin concentrations and exposure to phototherapy
No control group without hyperbilirubinemia ($n = 73$)		
	Ahdab-Barmada M et al. 1984	The neuropathology of kernicterus in the premature neonate. Diagnostic problems
	Ahlfors CE et al. 2003	Unbound bilirubin in a term newborn with kernicterus
	Ahlfors CE et al. 2008	Unbound bilirubin concentration is associated with abnormal automated auditory brainstem response for jaundiced newborns
	Alkén J et al. 2019	Rates of extreme neonatal hyperbilirubinemia and kernicterus in children and adherence to National Guidelines for screening, diagnosis, and treatment in Sweden
	Amin SB et al. 2001	Bilirubin and serial auditory brainstem responses in premature infants
	Amin SB et al. 2009	Hyperbilirubinemia and language delay in premature infants
	Amin SB et al. 2016	Unbound bilirubin and auditory neuropathy spectrum disorder in late preterm and term infants with severe jaundice
	Amin SB et al. 2017	Chronic auditory toxicity in late preterm and term infants with significant hyperbilirubinemia
	AlOtaibi SF et al. 2005	Neurological complications of kernicterus
	Amin SB et al. 2015	Unbound unconjugated hyperbilirubinemia is associated with central apnea in premature infants

(Continues)

TABLE A2 (Continued)

#	Study	Title
	Arun Babu T et al. 2011	Predictors of abnormal neurodevelopment at 6 months in term babies with early neonatal hyperbilirubinemia. A prospective cohort study from South India
	Arun Babu T et al. 2012	Association between peak serum bilirubin and neurodevelopmental outcomes in term babies with hyperbilirubinemia
	Chen W et al. 2006	Neurodevelopmental outcome of severe neonatal hemolytic hyperbilirubinemia
	Çolak R et al. 2020	The neurodevelopmental outcome of severe neonatal hemolytic and nonhemolytic hyperbilirubinemia
	Croen LA et al. 2005	Neonatal hyperbilirubinemia and risk of autism spectrum disorders
	De Vries LS et al. 1985	Relationship of serum bilirubin levels to ototoxicity and deafness in high-risk low-birth-weight infants
	De Vries LS et al. 1987	Relationship of serum bilirubin levels and hearing impairment in newborn infants
	Donneborg ML et al. 2020	Extreme neonatal hyperbilirubinemia and kernicterus spectrum disorder in Denmark during the years 2000–2015
	Dubey P et al. 2020	Neurodevelopmental outcome of healthy term newborn with serum bilirubin >15 mg/dL at 1 year
	Ebbesen F et al. 2012	Relation between serum bilirubin levels ≥450 μmol/L and bilirubin encephalopathy; a Danish population-based study
	ElTatawy S et al. 2020	The spectrum of bilirubin neurotoxicity in term and near-term babies with hyperbilirubinemia: Does outcome improve with time?
	Frank R et al. 2017	Clinical profile of children with cerebral palsy born term compared with late- and post-term: a retrospective cohort study
	Gharehbaghi MM et al. 2013	Determination of ASQ score in infants with neonatal hyperbilirubinemia and its relationship with total serum bilirubin levels and bilirubin albumin ratio
	Gordon et al., 2005	Neurological and developmental outcome of neonatal jaundice and sepsis in rural Kenya
	Grunebaum E et al. 1991	Breast mild jaundice: Natural history, familial incidence and late neurodevelopmental outcome of the infant
	Harris MC et al. 2001	Developmental follow-up of breastfed term and near-term infants with marked hyperbilirubinemia
	Heimler R et al. 2010	Neurodevelopmental and audiological outcome of healthy term newborns with moderately severe non-haemolytic hyperbilirubinemia
	Helal NF et al. 2019	Characteristics and outcome of newborn admitted with acute bilirubin encephalopathy to a tertiary neonatal intensive care unit
	Hulzebos CV et al. 2014	The bilirubin albumin ratio in the management of hyperbilirubinemia in preterm infants to improve neurodevelopmental outcome: A randomized controlled trial—BARTrial
	Hung KL et al. 1988	Auditory brainstem response in patients with a history of kernicterus
	Hyman CB et al. 1969	CNS abnormalities after neonatal hemolytic disease or hyperbilirubinemia. A prospective study of 405 patients
	Jangaard KA et al. 2008	Outcomes in a Population of Healthy Term and Near-Term Infants With Serum Bilirubin Levels of >325 μmol/L (>19 mg/dL) Who Were Born in Nova Scotia, Canada, Between 1994 and 2000
	Johnston WH et al. 1967	Erythroblastosis fetalis and hyperbilirubinemia. A five-year follow-up with neurological, psychological, and audiological evaluation
	Kitai Y et al. 2020	Diagnosis of bilirubin encephalopathy in preterm infants with dyskinetic cerebral palsy
	Kuzniewicz M et al. 2009	Interaction of hemolysis and hyperbilirubinemia on neurodevelopmental outcomes in the collaborative perinatal project
	Huang L et al. 2013	Neonatal bilirubin levels and childhood asthma in the US Collaborative Perinatal Project, 1959–1965
	Maimburg RD et al. 2008	Neonatal jaundice: a risk factor for infantile autism?
	Maimburg RD et al. 2010	Neonatal jaundice, autism, and other disorders of psychological development
	Maimburg RD et al. 2016	Neonatal hyperbilirubinemia and the risk of febrile seizures and childhood epilepsy
	Manning D et al. 2007	Prospective surveillance study of severe hyperbilirubinaemia in the newborn in the UK and Ireland
	McGillivray AJ et al. 2018	Long-term neurodevelopmental outcomes following extreme neonatal hyperbilirubinaemia in Australian infants born between 2010 and 2013
	Merhar SL et al. 2005	Clinical (video) findings and cerebrospinal fluid neurotransmitters in 2 children with severe chronic bilirubin encephalopathy, including a former preterm infant without marked hyperbilirubinemia

TABLE A2 (Continued)

#	Study	Title
	Miyazono Y et al. 2021	Nationwide survey of late-onset hemolysis in very low birthweight infants
	Morioka I et al. 2015	Current incidence of clinical kernicterus in preterm infants in Japan
	Mukhopadhyay K et al. 2010	Neurodevelopmental outcome of acute bilirubin encephalopathy
	Nakamura H et al. 1992	Determination of serum unbound bilirubin for prediction of kernicterus in low-birth-weight infants
	Nasiri J et al. 2018	The causes and risk factors in patients with kernicterus referred to the clinic of pediatric neurology during the years 2011 to 2016
	Nakamura H et al. 1985	Auditory nerve and brainstem responses in newborn infants with hyperbilirubinemia
	Newman TB et al. 1993	Neonatal hyperbilirubinemia and long-term outcome: Another look at the Collaborative Perinatal Project
	Ogunlesi TA et al. 2007	The incidence and outcome of bilirubin encephalopathy in Nigeria: A bi-centre study
	Oh W et al. 2010	Influence of clinical status on the association between plasma total and unbound bilirubin and death or adverse neurodevelopmental outcomes in extremely low birth weight infants
	Ošlejšková H et al. 2012	An association between neonatal jaundice and autism
	Paludetto R et al. 1986	Moderate hyperbilirubinemia does not influence the behaviour of jaundiced infants
	Paludetto R et al. 2002	Moderate hyperbilirubinemia induces a transient alteration of neonatal behavior
	Saini AG et al. 2021	Hyperbilirubinemia and asphyxia in children with dyskinetic cerebral palsy
	Saluja S et al. 2010	Auditory neuropathy spectrum disorder in late preterm and term infants with severe jaundice
	Scheidt PC et al. 1977	Toxicity to bilirubin in neonates: Infant development during first year in relation to maximum neonatal serum bilirubin concentration
	Seidman DS et al. 1991	Neonatal hyperbilirubinemia and physical and cognitive performance at 17 years of age
	Sgro M et al. 2011	Acute neurological findings in a national cohort of neonates with severe neonatal hyperbilirubinemia
	Sharma D et al. 2021	Early neurodevelopmental outcome of neonates with gestation 35 weeks or more with serum bilirubin in exchange range without encephalopathy: A prospective observational study
	Simmons JL et al. 2000	Auditory neuropathy: Case study with hyperbilirubinemia
	Smith CM et al. 2004	Auditory brainstem response detects early bilirubin neurotoxicity at low indirect bilirubin values
	Tsao PC et al. 2020	Long-term neurodevelopmental outcomes of significant neonatal jaundice in Taiwan from 2000–2003: A nationwide, population-based cohort study
	Van de Bor M et al. 1989	Hyperbilirubinemia in preterm infants and neurodevelopmental outcome at 2 years of age: Results of a national collaborative survey
	Vohr BR et al. 1989	Abnormal brain-stem function (brain-stem auditory evoked response) correlates with acoustic cry features in term infants with hyperbilirubinemia
	Vohr BR et al. 1990	Behavioral changes correlated with brain-stem auditory evoked responses in term infants with moderate hyperbilirubinemia
	Wennberg RP et al. 1982	Abnormal auditory brainstem response in a newborn infant with hyperbilirubnemia: Improvement with exchange transfusion
	Wolf MJ et al. 1997	Extreme hyperbilirubinaemia in Zimbabwean neonates: Neurodevelopmental outcome at 4 months
	Wolf MJ et al. 1998	Neurological status in severely jaundiced Zimbabwean neonates
	Wolf MJ et al. 1999	Neurodevelopmental outcome at 1 year in Zimbabwean neonates with extreme hyperbilirubinaemia

(Continues)

TABLE A2 (Continued)

#	Study	Title
	Yilmaz Y et al. 2001	Neurological prognosis in term newborns with neonatal indirect hyperbilirubinemia
	Yilmaz Y et al. 2001	Prognostic value of auditory brainstem response for neurologic outcome in patients with neonatal indirect hyperbilirubinemia
	Yuan X et al. 2019	Early amplitude-integrated electroencephalography predicts long-term outcomes in term and near-term newborns with severe hyperbilirubinemia
No neurodevelopmental outcome ($n = 6$)		
	Bhutani VK et al. 2001	Jaundice technologies. Prediction of hyperbilirubinemia in term and near term newborns
	Boggs T et al. 1967	Correlation of neonatal serum total bilirubin concentration and developmental status at age eight months. Preliminary report from the collaborative project
	Ding Y et al. 2021	High levels of unbound bilirubin are associated with acute bilirubin encephalopathy in post-exchange transfusion neonates
	Ku MS et al. 2012	Neonatal jaundice is a risk factor for childhood asthma: a retrospective cohort study
	Stevenson DK et al 2001	Prediction of hyperbilirubinemia in near-term and term infants
	Thielemans L et al. 2021	High levels of pathological jaundice in the first 24 hours and neonatal hyperbilirubinaemia in an epidemiological cohort study on the Thailand-Myanmar border
Other types of publication ($n = 1$)		
	Jeffrey M et al. 2001	Bilirubin and neurological dysfunction—Do we need to change what we are doing?
No data from control group ($n = 1$)		
	Newman TB et al. 2003	Infants with bilirubin levels of 30 mg/dL or more in a large managed care organisation
No separate data for full-term and pre-term neonates ($n = 6$)		
	Culley P et al. 1970	Sequelae of neonatal jaundice
	Ebbesen F et al. 2010	Neonatal non-hemolytic hyperbilirubinemia: a prevalence study of adult neuropsychiatric disability and cognitive function in 463 male Danish conscripts
	Kumar V et al. 2021	Childhood neurodevelopmental outcomes of survivors of acute bilirubin encephalopathy: A retrospective cohort study
	Lozada Le et al. 2015	Association of autism spectrum disorders with neonatal hyperbilirubinemia
	Newman TB et al. 2005	Outcomes among newborns with Total serum bilirubin levels of 25 mg per deciliter or more
	Wei CC et al. 2015	Neonatal jaundice and increased risk of attention-deficit hyperactivity disorder: a population-based cohort study

TABLE A3 Risk of bias for cohort and case–control studies measured with the Newcastle–Ottawa scale (NOS).

	Selection				Comparability	Outcome			
Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at the baseline	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Quality score
Agrawal et al., 1998	*	*	*	*	**	*	*	*	9 Good quality
Bengtsson & Verneholt, 1974	*	*	*	*	0	*	*	*	7 Good quality
Besli et al., 2020	*	*	*	*	**	*	*	*	9 Good quality
Can et al., 2015	*	*	*	*	*	0	*	*	7 Good quality
Y. Chen & Kang al., 1995	*	*	*	*	**	*	*	0	8 Good quality
Deorari et al., 1994	0	0	*	*	**	*	0	*	6 Fair quality
Grimmer et al., 1999	*	*	*	*	**	0	*	*	8 Good quality
Gupta et al., 1990	*	0	*	*	**	*	*	0	7 Good quality
Hokkanen et al., 2014	*	*	*	*	**	0	*	*	8 Good quality
Holmes et al., 1968	*	*	*	*	0	0	*	*	6 Fair quality
Hung, 1989	*	*	*	*	*	*	0	*	7 Good quality
Kahraman et al., 2021	*	*	*	*	**	*	*	*	9 Good quality

(Continues)

TABLE A3 (Continued)

Study	Selection				Comparability	Outcome			
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at the baseline	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Quality score
Lunsing et al., 2013	*	*	*	*	**	*	0	0	7 Good quality
Özmert et al., 1996	*	*	*	*	0	*	*	*	7 Good quality
Rubin et al., 1979	*	*	*	*	**	0	*	*	8 Good quality
Sabatino et al., 1996	*	0	*	*	0	*	*	*	6 Fair quality
de Almeida et al., 2002	*	*	*	*	0	*	0	0	5 Fair quality
Soorani-Lunsing et al., 2001	*	*	*	*	**	*	*	*	9 Good quality
Wong et al., 2006	*	0	*	*	**	0	*	*	7 Good quality

Note: One asterisk represents one point for the appraisal item, and two asterisks represent two points.

TABLE A4 Methodological quality measured via the MINCir scale.

Study	Domain 1 Item 1	Domain 2 Item 2	Domain 3				Total score	Quality score
			Item 3	Item 4	Item 5	Item 6		
Agrawal et al., 1998	4	2	3	2	3	1	15	Bad
Bengtsson & Verneholt, 1974	4	6	3	2	3	1	19	Good
Besli et al., 2020	4	2	3	2	3	1	15	Bad
Can et al., 2015	4	10	2	2	3	3	24	Good
Y. Chen & Kang, 1995	4	3	3	1	3	1	15	Bad
Deorari et al., 1994	4	2	2	2	3	1	14	Bad
Grimmer et al., 1999	3	2	2	1	3	1	12	Bad
Gupta et al., 1990	3	2	3	1	3	1	13	Bad
Hokkanen et al., 2014	4	6	3	2	3	1	19	Good
Holmes et al., 1968	3	3	3	1	3	1	14	Bad
Hung, 1989	3	3	3	3	3	1	16	Bad
Kahraman et al., 2021	3	4	3	2	3	3	18	Good
Lunsing et al., 2013	4	4	3	2	2	1	16	Bad
Özmert et al., 1996	3	4	3	2	3	1	16	Bad
Rubin et al., 1979	4	6	3	2	2	1	18	Good
Sabatino et al., 1996	4	3	2	1	3	1	14	Bad
de Almeida et al., 2002	4	3	3	2	2	1	15	Bad
Soorani-Lunsing et al., 2001	4	2	3	1	3	1	14	Bad
Wong et al., 2006	4	3	3	3	5	1	19	Good

TABLE A5 Characteristics of the sample and level of evidence quality in the included studies.

Reference, country and year	Sample size gender (female/male)			Birth weight (g)		Study population gestational age (week)		Design	Evidence level
	S	S-EG	S-CG	EG	CG	EG	CG		
Agrawal VK et al. India 1998	30 exposed	14/16	25	2630 ± 160	2650 ± 921	Full-term 4.2 days	Full-term 3.9 days	Prospective cohort	2b
Bengtsson B et al. Sweden 1974	111 exposed	34/77	115	>2500	>2500	Full-term 38 to 42	Full-term 38 to 42	NR	2b
Besli GE et al. Turkey 2020	41 exposed	18/23	12	3220.60 ± 449.21	≥2500	Full-term 40.10 ± 0.88	Full-term 18–24 months	Prospective cohort	2b
Can E et al. Turkey 2015	85 exposed	26/59	102	2876.16 ± 229.26	2916.16 ± 235.13	Preterm 35.2 ± 1.1	Preterm 35.5 ± 1.2	Prospective observational	2b
Chen YJ et al. Taiwan 1995	72 exposed	BG-low 12/14 BG-moderate 12/13 BG-severe 10/11	10/12	Low 345.6 ± 291.4[a] Moderate 3451.2 ± 216.6 Severe 3395.4 ± 256.4	3350.2 ± 241.8	Full-term Low 39.1 ± 1.0 Moderate 39.1 ± 1.0 Severe 39.4 ± 1.5	Full-term 39.5 ± 1.1	NR	2b
Deorari AK et al. India 1994	18 exposed	10/8	11/9	2300 to 3300	2600 to 3400	Full-term 39.0 ± 0.41	Full-term 39 ± 0.3	Prospective cohort	4
Grimmer I et al. Germany 1999	29 exposed	29	18	>2500	>2500	Full-term >37	Full-term >37	NR	2b
Gupta AK et al. India 1990	25 exposed	10/15	10/10	2680 ± 260	2840 ± 280	Full-term 40.4 ± 0.6	Full-term 40.8 ± 0.8	NR	2b
Hokkanen L et al. Finland 2014	128 exposed	Affected 22/35 Unaffected 32/39	40/30	BG-affected 3505 BG-unaffected 3469	3538	Full-term Affected 39.5 Unaffected 39.3	Full-term 39.8	Prospective cohort	2b
Holmes GE et al. United States 1968	63 exposed	High 23 Low 25 Streptomycin 13	17	>2500	>2500	Full-term NR	Full-term NR	NR	4

TABLE A5 (Continued)

Reference, country and year	Sample size gender (female/male)			Birth weight (g)		Study population gestational age (week)		Design	Evidence level
	S	S-EG	S-CG	EG	CG	EG	CG		
Hung KL China 1989	75 exposed	75	30 newborns 55 infants 59 older children	>2500	>2500	Full-term >37	Full-term >37	Retrospective and prospective cohort	2b
Kahraman A. Et al. Turkey 2021	30 exposed	9/21	11/19	2986 ± 674.6	3219 ± 434.4	Full-term 38.2 ± 0.8	Full-term 38.2 ± 0.8	Retrospective cohort	2b
Lunsing RJ et al. Netherlands 2013	43 exposed	17/26	35/35	3450 ± 617	3616 ± 456	Full-term 277 ± 9 days	Full-term 282 ± 10 days	Prospective cohort	2b
Ozmert E et al. Turkey 1996	102 exposed	31/71	10/17	>3000	>3000	Full-term >37	Full-term >37	Retrospective cohort	2b
Rubin RA et al. United States 1979	241 exposed	164 moderate bilirubin 77 high bilirubin	125 low bilirubin	Moderate 3214.97 ± 589.59 High 3003.21 ± 654.19	3373.89 ± 464.65	Full-term Moderate 39.69 ± 3.08 High 38.60 ± 2.79	Full-term 40.49 ± 2.55	NR	2b
Sabatino G et al. Italia 1996	48 exposed	28/20	22/18	3312 ± 411	3492 ± 501	Full-term 40.2 ± 1.1	Full-term 40.3 ± 1.6	NR	4
Sales de Almeida F et al. Brazil 2002	32 exposed	11/21	32	NR	NR	Full-term NR	Full-term NR	Clinical prospective	4
Soorani-lunsing I et al. Netherlands 2001	20 exposed	5/15	5/15	3480 ± 403	3357 ± 402	Full-term 272 ± 12 days	Full-term 278 ± 12 days	NR	2b
Wong V et al. China 2006	99 exposed	39/60	6/3	3171.2 ± 393.2	3087.8 ± 403.2	Full-term 38.71 ± 1.38	Full-term 39.1 ± 1.65	Prospective Cohort	2b

Abbreviations: BG, bilirubin group; CG, control group; EG, experimental group; NOS, Newcastle–Ottawa Scale; NR, not reported; S, sample.
[a]Typos in the selected article that the authors have not corrected.

TABLE A6 Characteristics of the intervention in the included studies.

Reference	Definition of hyperbilirubinemia	Treatment	Subjects in the active group	Age during treatment	Period	Frequency	Intensity	Application	Moment
Agrawal VK et al.	>15 mg/dL	Blood transfusions Phototherapy	14/30 16/30	NR	NR	NR	NR	NR	NR
Bengtsson B et al.	>20 mg/100 mL	Blood transfusions	44/111	NR	NR	NR	NR	NR	NR
Besli GE et al.	<20 mg/dL (Group I) 20–24.9 mg/dL (Group II), ≥25 mg/dL (Group III) ≥20 mg/dL and hemolytic disease (Group IV)	NR	NR	NR	NR	NR	NR	NR	NR
Can E et al.	Experimental group ≥20 mg/dL Control group <20 mg/dL	Phototherapy	187	NR	NR	NR	NR	NR	NR
Chen YJ et al.	Severe ≥20.11 mg/dL Moderate 15–20 mg/dL Low 10–14.9 mg/dL	Blood transfusions Phototherapy	18/21 (severe) 46/46 (mild + severe)	NR	NR	NR	NR	NR	NR
Deorari AK et al.	>15 mg/dL	Blood transfusions Phototherapy	7/18 NR	NR	NR	NR	NR	NR	NR
Grimmer I et al.	20–30 mg/dL	Blood transfusions Phototherapy	29/29 29/29 Median 21 h	NR	NR	NR	NR	NR	NR
Gupta AK et al.	20–35 mg/dL	Blood transfusions	One – 20/25 Two – 5/25	NR	NR	NR	NR	NR	NR
Hokkanen L et al.	20 mg/100 mL	Blood transfusions Phototherapy	79/128 54/128	NR	NR	NR	NR	NR	NR
Holmes GE et al.	>5.5 mg/100 cc	Blood transfusions	9/25 – High group 2/23 – Low group	NR	NR	NR	NR	NR	NR
Hung KL	High bilirubin (19–51 mg/dL)	Blood transfusions Phototherapy	26/75 39/75	NR	NR	NR	NR	NR	NR
Kahraman A. Et al.	>13.5 mg/dL	Blood transfusions Phototherapy	4/30 26/30	NR	NR	NR	NR	NR	NR
Lunsing RJ et al.	≥12.9 mg/dL	Phototherapy	NR	NR	NR	NR	NR	NR	NR
Ozmert E et al.	17–48 mg/dL	Blood transfusions	102/102	NR	NR	NR	NR	NR	NR
Rubin RA et al.	Moderate bilirubin (11–15 mg/dL) ($n = 164$) High bilirubin (16–23 mg/dL) ($n = 77$)	Blood transfusions	14/77 (high bilirubin)	NR	NR	NR	NR	NR	NR

TABLE A6 (Continued)

Reference	Definition of hyperbilirubinemia	Treatment	Subjects in the active group	Age during treatment	Period	Frequency	Intensity	Application	Moment
Sabatino G et al.	238–442 mM	Blood transfusions phototherapy	NR NR	NR	NR	NR	NR	NR	NR
Sales de Almeida F et al.	>10 mg/dL	NR	NR	NR	NR	NR	NR	NR	NR
Soorani-lunsing I et al.	>12.9 mg/dL	Phototherapy	10/20	NR	NR	NR	NR	NR	NR
Wong V et al.	Mild ≤30 mg/dL Severe ≤25 mg/dL Super ≥25 mg/dL	Blood transfusions phototherapy	3/99 99/99	NR	NR	NR	NR	NR	NR

NR, Not reported.

TABLE A7 Statistical analysis of the outcomes.

Reference	Assessed variables	Follow-up	*P*-value	Inter-group comparison	Neurodevelopmental disorder
Agrawal VK et al.	BAER DENVER (second edition)	Within the first week 1 year 1 year	$P < 0.05$ NR NR	E > C NR NR	Auditory alterations associated with global development
Bengtsson B et al.	Neurological examination physical examination Gross motor functions Fine motor functions Terman-Merrill test Hearing examination WIT test	6.5 to 13 years	NR	NR	Neurological and auditory disorders
Besli GE et al.	BAER DENVER Neurological examination	18 to 24 months 3 months 18 to 24 months	$P < 0.05$ $P > 0.05$ $P < 0.05$	E > C E = C E > C	Neurological and auditory disorders
Can E et al.	BAER Oto-acoustic emissions	Within the first week 1 year Within the first week	$P > 0.05$ $P > 0.05$ $P > 0.05$	E = C E = C E = C	No auditory neuropathy in late premature neonates treated with phototherapy
Chen YJ et al.	VEP (latency/amplitude) DENVER (first edition)	1 week 2 weeks 4 weeks 8 weeks 1 year	$P < 0.05/P < 0.05$ $P < 0.05/P > 0.05$ $P < 0.05/P > 0.05$ $P < 0.05/P > 0.05$ NR	E > C/E > C E > C/E = C E > C/E = C E > C/E = C NR	Visual alterations, hypotonia, and motor retardation
Deorari AK et al.	BAER DQ by Nancy Bayley Scale Audiometry	Every 24–48 h 1 month 6 months 12 months 6 months 12 months 6 months 12 months	$P > 0.05$ $P > 0.05$ $P > 0.05$ $P > 0.05$ $P > 0.05$ NR NR NR	E > C E > C E > C E > C E > C NR NR NR	Auditory alterations that subsided following blood transfusions
Grimmer I et al.	Touwen examination	7 years	$P > 0.1$	E = C	Neurological alterations
Gupta AK et al.	BAER (latency)	Newborn 3 months	$P < 0.05$ (2/3) $P > 0.05$	E > C (2/3) E = C	Auditory alterations

(Continues)

TABLE A7 (Continued)

Reference	Assessed variables	Follow-up	*P*-value	Inter-group comparison	Neurodevelopmental disorder
	APGAR 1 min	6 months	$P > 0.05$	E = C	
	APGAR 5 min	Newborn	NR	NR	
		Newborn	NR	NR	
Hokkanen L et al.	WISC	9 years	$P < 0.0001$	E > C	Neurological and cognitive alterations
	ITPA	9 years	$P < 0.0001$	E > C	
	Reading test	9 years	$P < 0.003$	E > C	
	Spelling test	9 years	$P < 0.0001$	E > C	
	Neurodevelopmental screening method by Michelsson	9 years	NR	NR	
		9 years	NR	NR	
		At birth	$P > 0.05$	E = C	
	Test of motor impairment	At birth	$P < 0.002$	E > C	
	APGAR 1 min	At birth	$P > 0.05$	E = C	
	APGAR 5 min				
	APGAR 10 min				
Holmes GE et al.	Audiometry	4 to 7 years	NR	NR	No long-term complications
	Modified Oseretsky test	4 to 10 years	NR	NR	
	Physical examination	4 to 7 years	NR	NR	
Hung KL	BAER	1 month	NR	NR	Auditory alterations
		1 year	NR	NR	
Kahraman A. Et al.	GMA	3 and 5 months	$P < 0.05$	E > C	Motor alterations
Lunsing RJ et al.	Prechtl's neurological examination	3–8 days	NR	NR	Neurological alterations
		3 months	NR	NR	
	GMA	18 months	NR	NR	
	Neurologic examination of Hempel	18 months	NR	NR	
		18 months	NR	NR	
	Screening method by Amiel–Tison				
	Toddler Behavior Assessment Questionnaire				
	APGAR 1 min				
Ozmert E et al.	VEP	8 to 13 years	$P > 0.05$	E = C	Auditory alterations associated with neurological conditions and certain cases of cognitive impairment
	BAER		$P < 0.05$ (3/6)	E > C (3/6)	
	WISC-R		$P < 0.05$ (2/6)	E > C (2/6)	
	Physical examination		$P > 0.05$	E = C	
	Neurological examination		$P < 0.05$ (2/6)	E > C (2/6)	
Rubin RA et al.	APGAR	1 min after birth	$P > 0.05$	E = C	Motor alterations at 8 months and neurological alterations at 1 year
	Bayley Scales of Mental and Motor Development	5 min after birth	$P > 0.05$	E = C	
		8 months	Mental $p > 0.05$	E = C	
	Stanford–Binet, Short Form L-M	4 years	Motor $p < 0.05$	E > C	
		7 years	$P > 0.05$	E = C	
	WISC	5 years	$P > 0.05$	E = C	
	Metropolitan Readiness Tests	6 years	$P > 0.05$	E = C	
	ITPA	5 years	$P > 0.05$	E = C	
	Neurologic examinations	6 years	$P > 0.05$	E = C	
		12 months	$P > 0.05$	E = C	
		7 years	$P < 0.05$	E > C	
			$P > 0.05$	E = C	
Sabatino G et al.	BAER	3, 5–7 days	NR	NR	Auditory alterations
	Brunett–Lezine test	3, 6, 12 weeks	NR	NR	
		6 months	NR	NR	
		18 months	NR	NR	
		30 months	NR	NR	
Sales de Almeida F et al.	BAER	1 to 24 days	$P < 0.05$	E > C	Auditory alterations
	Oto-acoustic emissions	1 to 24 days	$P > 0.05$	E = C	

TABLE A7 (Continued)

Reference	Assessed variables	Follow-up	*P*-value	Inter-group comparison	Neurodevelopmental disorder
Soorani-lunsing I et al.	Prechtl's Neurological Examination GMA Behavior Questionnaire	3 to 8 days 12 months 3 months	$P < 0.05$ $P < 0.05$ 0.05	E > C E > C E = C	Neurological alterations
Wong V et al.	BAER Physical examination Neurologic examination Visual examination	Every 3 to 6 months until the age of 3 years	$P > 0.05$ $P > 0.05$ $P > 0.05$ $P > 0.05$	E = C E = C E = C E = C	No alterations

Abbreviations: BAER, Brainstem auditory evoked response; C, control group; CRIB, clinical risk index of babies; DENVER, Denver Developmental Screening Test; DQ, Development quotient; E, experimental group; GMA, General Movements Assessment; ITPA, Illinois Test of Psycholinguistic Abilities; NR, not reported; VEP, visual evoked potentials; WISC-R, Wechsler Intelligence Scale for Children—Revised.