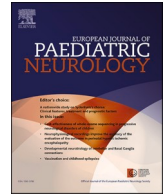


Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

European Journal of Paediatric Neurology

journal homepage: www.journals.elsevier.com/european-journal-of-paediatric-neurology

Review Article

Predictive value of brain MRI for neurodevelopmental outcome in infants with severe unconjugated hyperbilirubinemia: A systematic review

Noortje M. van der Meulen^{a,*}, Karin L. Meijers^{b,1}, Jeroen Dudink^b, Laura A. van de Pol^c^a Emma Children's Hospital, Amsterdam University Medical Center, Meibergdreef 9, 1105AZ, Amsterdam, the Netherlands^b Wilhelmina Children's Hospital, University Medical Center Utrecht, Lundlaan 6, 3584EA, Utrecht, the Netherlands^c Department of Child Neurology, Amsterdam University Medical Center, Amsterdam Neuroscience Vrije Universiteit, De Boelelaan 1117, 1081HV, Amsterdam, the Netherlands

ARTICLE INFO

Keywords:

MRI
Hyperbilirubinemia
(Pre-)term infants
Neurodevelopmental outcome
Kernicterus

ABSTRACT

Context: Debate exists regarding predictive value of brain MRI for long-term neurodevelopmental outcome (NDO) in infants with severe unconjugated hyperbilirubinemia (above exchange transfusion levels).**Objective:** To investigate whether MRI findings among (pre-)term infants with severe unconjugated hyperbilirubinemia can predict NDO at ≥ 12 months and determine optimal timing for MRI.**Data sources:** PubMed and Embase. Last update: June 14, 2024.**Study selection:** Studies in which (pre-)term infants with severe unconjugated hyperbilirubinemia who underwent an MRI before 24 months and had a reported NDO at ≥ 12 months were included.**Data extraction:** Patient characteristics, MRI and NDO details were extracted.**Results:** The search yielded 732 studies, of which 22 were included. Individual patient information was obtained for 120 infants (MRI-timing: early (≤ 6 weeks) $n = 75$, late (> 6 weeks) $n = 19$, unknown $n = 26$). Positive predictive value (PPV) of abnormal MRI in the total group for impaired NDO was high (77.5 %). The PPV of late compared to early MRI was much higher, 92.3 % versus 71.7 %. Negative predictive value of normal MRI for normal NDO in the total group was low (29.0 %) and again higher in late compared to early MRI, 50.0 % versus 27.3 %.**Limitations:** Quantitative synthesis of results was impossible due to large heterogeneity in study designs. Furthermore, selection bias towards patients with impaired outcome might have influenced our results.**Conclusions:** Brain MRI can serve as prognostic tool for NDO in infants with severe unconjugated hyperbilirubinemia, both in early and late stages, but each timing has inherent constraints. Further prospective studies are necessary.

1. Introduction

Jaundice caused by slightly increased bilirubin levels is a common condition in newborns; in most cases, it is harmless. However, current screening practices, especially when solely based on visual inspection, may contribute to the occurrence of severe hyperbilirubinemia. When this happens, and the unbound bilirubin concentration significantly increases, the condition can potentially lead to neurotoxicity [1]. The early-stage manifestations of this complication can present as acute bilirubin encephalopathy (ABE) [2]. Alarming, this condition is linked to a mortality rate as high as 20.4 % [3].

Early diagnosis and intervention are the keys to mitigating the effects

of hyperbilirubinemia. However, because of the commonly benign nature of neonatal jaundice and because visual inspection of jaundiced skin cannot predict high total serum bilirubin (TSB) levels, the severity of the condition can be underestimated [4]. In fact, the subtle progression of unconjugated hyperbilirubinemia to hazardous levels can go unnoticed by caregivers and even medical professionals. Due to the fact that symptoms of hyperbilirubinemia may be subtle or underrecognized, severe hyperbilirubinemia can occur before clinical signs manifest.

Survivors of ABE often face chronic repercussions due to the toxic effects of bilirubin on several parts of the central nervous system, a condition now recognized as kernicterus spectrum disorder (KSD) [5]. Typical brain regions with neural damage caused by hyperbilirubinemia are mainly the globus pallidus and sub-thalamic nuclei. Furthermore,

* Corresponding author. Meibergdreef 9, 1105AZ, Amsterdam, the Netherlands.

E-mail address: n.m.vandermeulen@amsterdamumc.nl (N.M. van der Meulen).¹ contributed equally as co-first authors.<https://doi.org/10.1016/j.ejpn.2024.09.010>

Received 7 April 2024; Received in revised form 24 September 2024; Accepted 27 September 2024

Available online 27 September 2024

1090-3798/© 2024 The Authors. Published by Elsevier Ltd on behalf of European Paediatric Neurology Society. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Abbreviations

ABE =	acute bilirubin encephalopathy
ABR =	auditory brainstem response
ADC =	apparent diffusion coefficient
aEEG =	amplitude integrated electroencephalography
ALFF =	amplitude of low frequency fluctuations
BE =	bilirubin encephalopathy
BIND =	bilirubin-induced neurological dysfunction
DWI =	diffusion-weighted imaging
fMRI =	functional magnetic resonance imaging
FLAIR =	fluid-attenuated inversion recovery
KSD =	kernicterus spectrum disorder
MRI =	magnetic resonance imaging
MRS =	magnetic resonance spectroscopy
NDO =	neurodevelopmental outcome
NPV =	negative predictive value
PPV =	positive predictive value
PRISMA =	preferred reporting items for systematic reviews and meta analyses
SWI =	susceptibility-weighted imaging
TSB =	total serum bilirubin

neural damage is described in the hippocampus, oculomotor nuclei, ventral cochlear nuclei and the Purkinje cells and dentate nuclei of the cerebellum [3]. Also, the auditory nerve and spiral ganglion containing cell bodies of primary auditory neurons can be involved [6].

Despite aggressive treatment protocols and increased awareness, the incidence of this condition is still 0.8–2.3 per 100,000 births [7–9]. The consequences of KSD are far-reaching, resulting in neurodevelopmental disabilities ranging from mild to very severe, including dyskinetic cerebral palsy and/or hearing loss, vertical gaze palsy, and cognitive impairment [2]. Early diagnosis of KSD is important for several reasons. It can aid in better prognostic prediction and therapeutic planning. Individualized management strategies can be tailored to ensure optimal care for affected infants via neurorehabilitative approaches that, when initiated during infancy (a period of significant brain plasticity), can yield the most substantial benefits. Such strategies can include physiotherapy, hearing aids and cochlear implants, speech therapy, and psychological support [3].

Magnetic resonance imaging (MRI) plays a significant role in early diagnosis in neonatal neuropathology. Because of the distinct characteristics often observed in children with bilirubin encephalopathy (BE), brain MRI is a commonly used diagnostic tool for both the acute phase and in KSD [10]. The classical MRI feature of BE is an abnormal pattern of a symmetrical, bilateral, abnormal signal particularly within regions of the globus pallidus and subthalamic nucleus. Interestingly, the nature of these characteristic signal abnormalities changes over time. In the acute or early phase of BE a high signal intensity is typically observed in T1-weighted images [11,12], whereas in the more chronic phase, the same pattern shifts to T2-weighted images [13–15]. These distinct MRI findings are illustrated in Fig. 1.

While the existing neuroimaging literature provides significant insights, a gap persists regarding how effectively MRI findings predict long-term neurodevelopmental outcome (NDO) and questions also remain about the most appropriate timing for MRI scans in this group of patients.

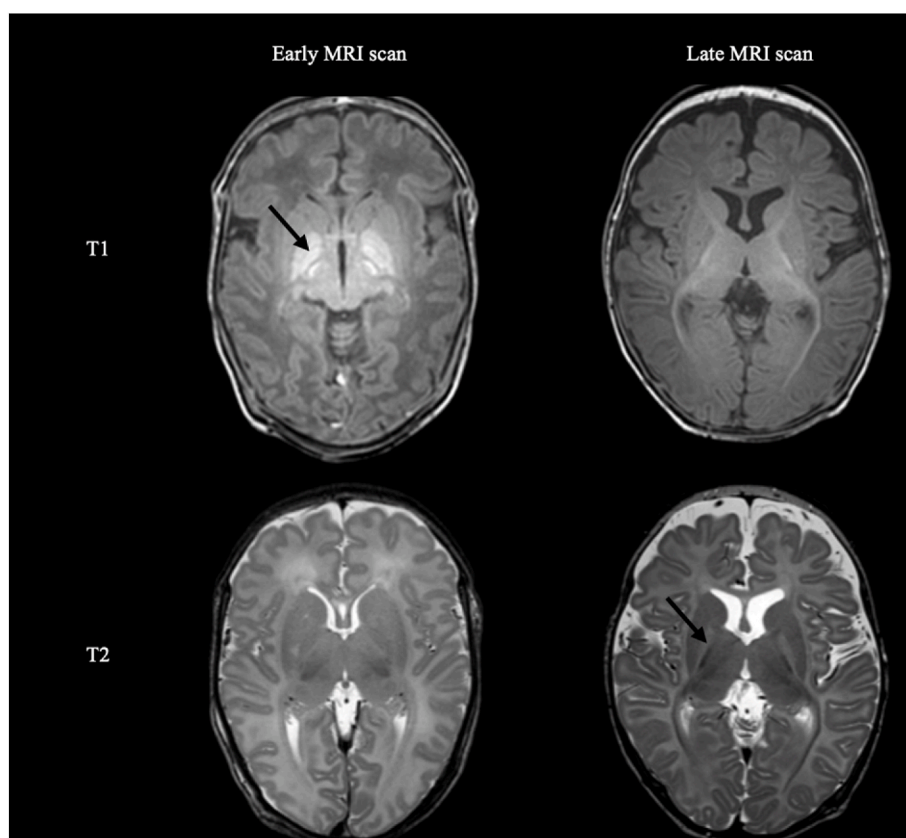


Fig. 1. Early versus late MRI scan

Figure showing early and late T1-and T2 weighted MRI scans of a patient with severe unconjugated hyperbilirubinemia.

Early MRI scan was made at 1 week, late MRI scan was made at 3 months.

*The arrows point out the hyperintensity of the globus pallidus (early MRI T1 and late MRI T2).

The objective of this systematic review was to examine whether MRI findings in pre-term and term infants with severe unconjugated hyperbilirubinemia can predict NDO at a minimum (corrected) age of 12 months. Additionally, we aimed to investigate the optimal timing for performing a brain MRI in relation to the outcome.

2. Materials and methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement and registered in PROSPERO under the registration number CRD42020185554.

2.1. Search

PubMed and Embase were systematically searched and the search strategy can be found in [Appendix A](#). Embase data were filtered for use in Embase and Embase/MEDLINE. Furthermore, in Embase, we filtered the studies according to publication type, and we only included articles and articles in press. The literature search was last updated on June 14, 2024.

2.2. Inclusion and exclusion criteria

We included studies in which pre-term (gestational age <37 weeks) and term (gestational age between 37 and 42 weeks) infants with severe unconjugated hyperbilirubinemia (above exchange transfusion levels) who underwent brain MRI before the age of 24 months and had a reported NDO at a minimum age of 12 months were reported. For pre-term infants the corrected age was used.

We excluded studies published in languages other than English, studies that did not assess the association between MRI findings and NDO and studies that included patients with other factors that could influence NDO (hypoxic-ischemic encephalopathy, meningitis, metabolic disorders, (trauma leading to) massive bleeding, congenital disorders). Frequent complications in pre-terms at the NICU department such as sepsis, that do not directly influence the neurodevelopmental outcome, were not part of the exclusion criteria.

2.3. Study selection

Two authors (K.M. and N.M.) independently screened all titles and abstracts using Rayyan [16]. Subsequently, the same authors evaluated the full texts, adhering to the predefined inclusion and exclusion criteria. Any disagreements were resolved through consensus reached via discussion. If necessary, additional reviewers (J.D. and L.P.) were consulted.

2.4. Data collection process

The data from the included studies were extracted by K.M. and N.M. The full texts were equally divided with regard to extracting data and the authors subsequently checked each other. The studies were divided into studies that presented individual patient data and those that presented patient data combined as a group. Any discrepancies in their judgements were resolved by double-checking the study or by discussion. In case of disagreements additional reviewers (J.D. and L.P.) were consulted. If specific data were missing (i.e., timing of MRI, age at follow-up) the study authors were contacted via email. All individual patient data and combined data were collected in a database. Patient characteristics and outcomes of the individual patient data were pooled as if they came from one study.

2.5. Data items

Regarding outcome measures, our focus was on obtaining data

related to NDO and MRI results. NDO data were considered if they were measured at a minimum age of 12 months. The data were categorized into three domains: motor impairment, cognitive impairment and auditory impairment.

Given the potential heterogeneity among the studies, we adopted a binary scoring system for these outcomes, distinguishing between impaired and not impaired. If an outcome in one of those domains was not mentioned in the original paper, the patient was not included in this specific subanalysis. In our study, we considered brain MRI scans that were conducted before the age of 24 months. We divided the patients into two categories based on their age at the time of their first MRI: “early” MRI made ≤ 6 weeks and “late” MRI made > 6 weeks. For patients who underwent multiple MRI scans, we compiled all pertinent information from these subsequent follow-up MRIs. For our analysis, we primarily utilized the first MRI performed, while subsequent MRIs were described separately. If the timing of MRI was not mentioned, the infant was not included in this specific subanalysis.

To address potential heterogeneity, the MRI outcomes were binary scored as normal or abnormal based on abnormalities observed in the basal ganglia, specifically signal abnormalities in the globus pallidus and/or subthalamic nucleus. Furthermore, we documented the MRI sequences.

In studies that presented individual patient data, only infants who met the inclusion criteria were selected for our review.

The other variables collected included the country, study design, cohort year, aim of the study and inclusion and exclusion criteria. Patient characteristics included were sex, gestational age, age at presentation and last follow-up, highest bilirubin levels, clinical picture at presentation, cause/risk factors for hyperbilirubinemia and intervention (phototherapy/exchange transfusion). These data were collected in a data form.

2.6. Risk of bias

Since we only selected infants from the included studies who met our inclusion criteria and analyzed them as a group, we did not perform a risk of bias assessment.

2.7. Effect measures/synthesis methods

Given that the studies exhibited dissimilarities, conducting a meta-analysis was deemed unsuitable. To assess the association between MRI findings and NDO, we adopted a 2x2 cross-tabulation method, utilizing the binary scores, to calculate positive and negative predictive values. For this analysis, we employed IBM SPSS Statistics, version 28.0.1.1.

3. Results

Our search yielded 732 records. After duplicate removal, 528 records were screened and 130 were selected for full-text screening. Ultimately, 22 studies were included in the review; 19 studies presented data for individual patients and three studies presented data combined as a group. The study selection process and reasons for exclusion can be found in [Fig. 2](#).

3.1. Study characteristics

The characteristics of the included studies are described in [Table 1](#). The study types varied: prospective cohort studies ($n = 5$), retrospective cohort studies ($n = 3$), case control studies ($n = 4$), case reports/case series ($n = 9$) and one double cohort study. Most of the studies included more patients than those presented in this table; however, we only present the data of the patients meeting our inclusion criteria. The last three studies, van Toorn et al. [34], Yuan et al. [35] and Mukhopadhy et al. [36] described their results for the group as a whole, and therefore

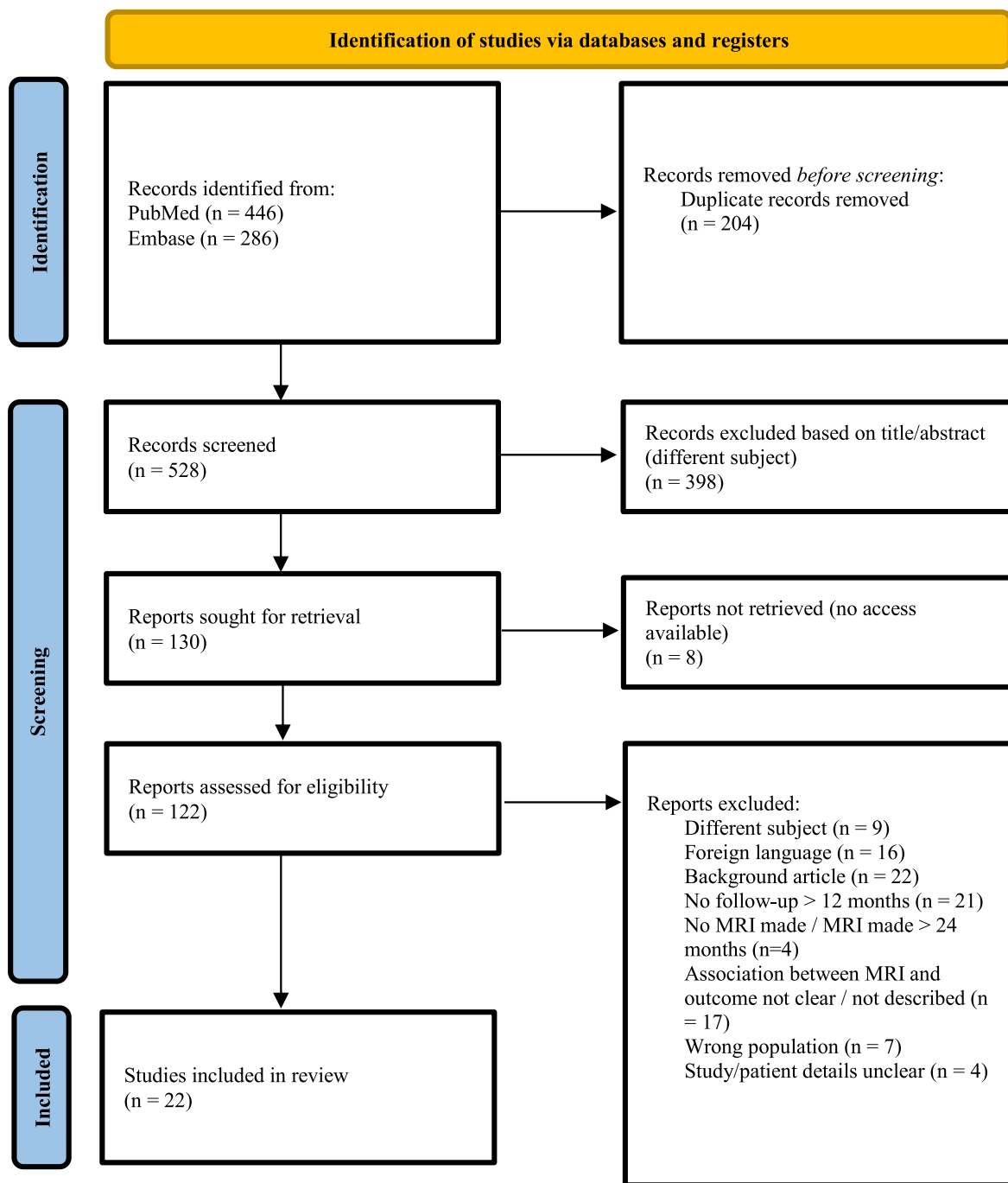


Fig. 2. Flowchart of the study selection.

could not be included in our individual patient data analyses. These studies will be discussed separately.

3.2. Results of individual studies

Individual patient information was obtained for 120 infants in total. Clinical follow-up timing varied from one to 16 years. In all patients, at least one MRI was made. Nineteen patients (25.8 %) underwent two MRIs, twelve patients (10.0 %) underwent three MRIs in total. Some studies did not report the exact timing of the first MRI performed (however, from the follow-up duration or the description in the article, it could be ascertained that the MRI was performed before the age of two years).

Description of MRIs among all studies was very heterogeneous, see

Table 1.

In 89 of the 120 infants (74.2 %) brain MRI was abnormal. Description of NDO and the methods of neurodevelopmental testing were also very heterogeneous among the studies, as seen in Table 1. In 91 of the 120 infants (75.8 %), NDO was described as impaired. Some studies defined NDO as normal or abnormal without specifying what outcome measurement was used or lacking information regarding sub-domains (motor impairment/auditory impairment/cognitive impairment) or severity. As a result patients with minor, moderate or severe neurological dysfunction were all combined in this group with an impaired NDO. Other studies provided a very detailed description per domain. Due to this heterogeneity, it was not possible to perform subgroup analysis based on the type or severity of MRI abnormalities or NDO.

Table 1
Study characteristics.

Author, (publication year), Country	Study Type	Cohort year	Number of patients included in original study	Included patients in this review (f/m)	Gestational age	Included serum bilirubin levels (μmol/L)	MRI sequence	MRIs made per patient (range)	Age first MRI (early/late) ^a	MRI abnormal	Abn MRI details	Age at last follow-up (range)	How was NDO measured?	NDO impaired at follow-up	Abn NDO details
Oakden et al. (2005) [17], Canada	Case control study	nm	6	6 (3f/3m)	Term	479–773	T1, T2, H-MRS	1	nm	Yes, n = 6 (100 %)	Abn SI GP T1, n = 6	1y	nm	Yes, n = 4 (66.7 %) No, n = 2 (33.3 %)	CP, n = 2, impaired hearing, n = 1, deafness, n = 1
Groenendaal et al. (2004) [18], The Netherlands	Case series	1997–2007	5	5 (sex nm)	Term	441–812	T1, T2, DWI, H-MRS	1	Early, n = 5 (100 %)	Yes, n = 4 (80 %) No, n = 1 (20 %)	Abn GP, n = 4	1-2y	Examinations of Amiel-Tison, Touwen, and the AIMS, GMDS, and classification of Hagberg et al.	Yes, n = 2 (40 %) No, n = 3 (60 %)	Truncal hypotonia + stereotyped movements, n = 1, Athetoid CP, n = 1
Harris et al. (2001) [19], USA	Retrospective cohort study	1993–1996	6	5 (sex nm)	Term	451–615	T1, T2	1-2	Early, n = 3 (60 %) Late, n = 2 (40 %)	Yes, n = 2 (40 %) No, n = 3 (60 %)	↑ SI GP T1, n = 1, ↑ SI putamen, DN bil, n = 1	3.5-6y	Neurological examinations, behavioral hearing examinations, BSID, yielding a mental developmental index and psychomotor developmental index	Yes, n = 1 (20 %) No, n = 4 (80 %)	Hearing loss >60 dB bil
Sgro et al. (2012) [7], Canada	Prospective, cohort study	2007–2008	20	12 (sex nm)	Pre-term – Term	429–795	nm	1	Early, n = 12 (100 %)	Yes, n = 10 (83.3 %) No, n = 2 (16.7 %)	↑ SI GP and SN, n = 10	1-3.3y	Hearing: ABR	Yes, n = 9 (75 %) No, n = 3 (25 %)	Very detailed and heterogeneous patient population, see reference
Yilmaz et al. (2001) [20], Spain	Case series	nm	10	4 (3f/1m)	Term	503–718	T1, T2	1	Late, n = 4 (100 %)	Yes, n = 4 (100 %)	↑ SI GP T2, n = 4	1.3-2y	Through physical and neurologic examinations. Developmental status, BERA	Yes, n = 4 (100 %)	Very detailed and heterogeneous patient population, see reference
Nickisch et al. (2009) [21], Germany	Case control study	2002–2006	30	7 (sex nm)	Pre-term – Term	386–770	nm	1	nm	Yes, n = 6 (85.7 %) No, n = 1 (14.3 %)	Typical BE, n = 6	1-9y	Behavioural audiometry, TEOAE, ABR	Yes, n = 7 (100 %)	Very detailed and heterogeneous patient population, see reference
Hansen et al. (2009) [22], Norway	Case series	nm	6	4 (f)	Term	477–792	nm	1	Early, n = 2 (50 %), nm, n	Yes, n = 2 (50 %) No, n = 2 (50 %)	↑ SI GP, n = 2	1.4-9y	nm	Yes, n = 2 (50 %) No, n = 2 (50 %)	Speech delay, n = 2

(continued on next page)

Table 1 (continued)

Author, (publication year), Country	Study Type	Cohort year	Number of patients included in original study	Included patients in this review (f/m)	Gestational age	Included serum bilirubin levels (μmol/L)	MRI sequence	MRIs made per patient (range)	Age first MRI (early/late) ^a	MRI abnormal	Abn MRI details	Age at last follow-up (range)	How was NDO measured?	NDO impaired at follow-up	Abn NDO details
Wu et al. (2015) [23], China	Double cohort study	1995–2011	93	2 (sex nm)	Pre-term	≥770, for both patients	nm	1–2	= 2 (50 %) Late, n = 2 (100 %)	Yes, n = 2 (100 %)	bil GP, SN, DN injury, n = 1, bil GP, PWM injury, n = 1	2.9–9.4y	nm	Yes, n = 2 (100 %)	Quadriplegic CP, n = 2
Gkoltsiou et al. (2008) [24], UK	Retrospective cohort study	1977–2005	11	8 (4f/4m)	Pre-term – Term	423–720	T1, T2, FLAIR	1–3	Early, n = 8 (100 %)	Yes, n = 7 (87.5 %) No, n = 1 (12.5 %)	Very detailed, see reference	1.4–3.5y	GMDS, HINE, ABR, and audiometry	Yes, n = 6 (75 %) No, n = 2 (25 %)	Very detailed and heterogeneous patient population, see reference CP, n = 11, impaired hearing, n = 4, deafness, n = 3, death, n = 2
Wang et al. (2008) [25], China	Case control studies	nm	31	22 (10f/12m)	Pre-term – Term	366–983	T1, T2, H-MRS, DWI	1	Early, n = 22 (100 %)	Yes, n = 17 (77.3 %) No, n = 5 (22.7 %)	↑ SI GP + SN, n = 9, ↑ SI GP, n = 8	At least 1y (2 patients died)	Hearing: BAEP	Yes, n = 20 (90.9 %) No, n = 2 (9.1 %)	Developmental delay, n = 2, impaired hearing, n = 3, CP, n = 3, death, n = 1
Wu et al. (2013) [26], USA	Case control study	nm	28	11 (5f/6m)	Term	357–727	T1, T2, H-MRS	1	nm	Yes, n = 11 (100 %)	↑ SI GP T1, n = 11	At least 2y (1 patient died)	nm	Yes, n = 9 (81.8 %) No, n = 2 (18.2 %)	Developmental delay, n = 2, impaired hearing, n = 3, CP, n = 3, death, n = 1
Merhar et al. (2005) [27], USA	Case report	nm	2	1 (f)	Term	845	T1, T2	2	Early	No	↑ SI GP T2 bil	13y	Hearing: ABR	Yes	Rigid tone, no language, no meaningful use of her limbs, partially dependent on TPN
Atalar et al. (2006) [28], Turkey	Case report	nm	2	2 (1f/1m)	Term	547–650	T1, T2, FLAIR	1	Late, n = 2 (100 %)	Yes, n = 2 (100 %)	↑ SI GP T2 + FLAIR bil, n = 1, ↑ SI GP + SN T2 bil, n = 1	1–1.3y	Neurological examinations	Yes, n = 2 (100 %)	Dyskinetic CP, n = 1, choreoathetosis, mental and motor retardation, dystonia and muscle rigidity, n = 1
Yilmaz et al. (2002) [29], Turkey	Case report	nm	1	1 (m)	Pre-term	599	T1, T2	1	Late	Yes	↑ SI GP + thal T2 bil, n = 1	1.3y	Neurological examinations	Yes	Dyskinetic CP, limitation of vertical gaze movement, growth/developmental delay

(continued on next page)

Table 1 (continued)

Author, (publication year), Country	Study Type	Cohort year	Number of patients included in original study	Included patients in this review (f/m)	Gestational age	Included serum bilirubin levels (μmol/L)	MRI sequence	MRIs made per patient (range)	Age first MRI (early/late) ^a	MRI abnormal	Abn MRI details	Age at last follow-up (range)	How was NDO measured?	NDO impaired at follow-up	Abn NDO details
Parashari et al. (2009) [30], India	Case report	nm	1	1 (sex nm)	Term	684	T2, FLAIR	1	Late	Yes	↑ SI GP T1 + FLAIR bil, n = 1	1y	Hearing: BERA	Yes	Seizures, abnormal movements, severe sensorineural hearing loss
Abe (2021) [31], Japan	Case report	nm	1	1 (m)	Pre-term	352	T1, T2	1	Late	No	–	1y	nm	No	–
Donneborg et al. (2020) [8], Denmark	Retrospective cohort study	2000–2015	408	7 (3f/4m)	Pre-term – Term	588–932	T1, T2	1	Early, n = 4 (57.1 %) Late, n = 3 (42.9 %)	Yes, n = 2 (28.6 %) No, n = 5 (71.4 %)	↑ SI GP, n = 2	2.5–16y	nm	Yes, n = 7 (100 %)	Very detailed and heterogeneous patient population, see reference
Gburek-Augustat et al. (2023) [32], Germany	Retrospective case study	2012–2022	8	3 (1f/2m)	Pre-term/nm	428–622	T1, T2, FLAIR	1–3	Early, n = 1 (33.3 %) Late, n = 2 (66.7 %)	Yes, n = 2 (66.7 %) No, n = 1 (33.3 %)	↑ SI GP T1, n = 1, ↑ SI GP T2 + FLAIR, n = 1	6–13y	GMFCS, BFMF, VSS	Yes, n = 3 (100 %)	Mild dyskinetic CP, n = 1, dyskinetic CP, vertical gaze palsy, enamel dysplasia, deafness and dysphagia, n = 1, dyskinetic CP, vertical gaze palsy and deafness treated with hearing aids, n = 1 KSD, n = 6, death, n = 4
Gelineau-Morel et al. (2024) [33], Nigeria	Prospective cohort study	2020	25	18 (9f/9m)	Pre-term – Term	296–679	T1, T2	1–3	Early, n = 17 (94.4 %) Late, n = 1 (5.6 %)	Yes, n = 13 (72.2 %) No, n = 5 (27.8 %)	Partial ↑ SI GP T1, n = 5, ↑ SI GP T1, n = 7, partial ↑ SI GP T2, n = 1	1y	BADS, Modified KSD toolkit, ABR	Yes, n = 10 (55.6 %) No, n = 8 (44.4 %)	
Van Toorn et al. (2016) [34], South-Africa	Prospective cohort study	2009–2013	30	25	nm	480–900	T1, T2	1	Early, n = 3 (12 %) Late, n = 22 (88 %)	Yes, n = 20 (80 %) No, n = 5 (20 %)	Very detailed, see reference	1.2–12.7y	nm	nm	Very detailed and heterogeneous patient population, see reference
Yuan et al. (2019) [35], China	Prospective cohort study	nm	77	40	Term	575–681	T1, T2	1	Early, n = 40 (100 %)	Yes, n = 12 (30 %) No, n =	Very detailed, see reference	1y	BSID (Second Edition), ABR	Yes, n = 11 (27.5 %) No, n =	Very detailed and heterogeneous patient

(continued on next page)

Table 1 (continued)

Author, (publication year), Country	Study Type	Cohort year	Number of patients included in original study	Included patients in this review (f/m)	Gestational age	Included serum bilirubin levels (μmol/L)	MRI sequence	MRIs made per patient (range)	Age first MRI (early/late) ^a	MRI abnormal	Abn MRI details	Age at last follow-up (range)	How was NDO measured?	NDO impaired at follow-up	Abn NDO details
Mukhopadhyay et al. (2010) [36], India	Prospective cohort study	nm	25	6	Term	474–788	T1	1	Early, n = 6 (100 %)	Yes, n = 5 (83.3 %)	Very detailed, see reference	1y	DDST-I, Amiel-Tison method, BERA	29 (72.5 %) Yes, n = 1 (16.7 %) No, n = 5 (83.3 %)	population, see reference Very detailed and heterogeneous patient population, see reference

Abbreviations: Abn, abnormal; ABR, Auditory Brainstem Response; AIMS, Alberta Infant Motor Scale; BADEP, Brainstem Auditory Evoked Potential; BE, Bilirubin Encephalopathy; BERA, Brainstem Evoked Response Audiometry; BFMF, Bimanual Fine Motor Function; bil, bilateral; BSID, Bayley Scales of Infant Development; CP, Cerebral Palsy; DDST, Denver Development Screening Test; DN, Dentate Nuclei; DWI, Diffusion-Weighted Imaging; f, female; FLAIR, Fluid-Attenuated Inversion Recovery; GMDS, Griffith's Mental Development Scales; GMFCS, Gross Motor Function Classification System; GP, Globus Pallidus; HINE, Hammersmith Infant Neurological Examination; H-MRS, Proton Magnetic Resonance Spectroscopy; m, male; nm, not mentioned; PWM, Periventricular White Matter; SI, Signal Intensity; SN, Subthalamic Nuclei; TFOAE, Transient Evoked Otoacoustic Emissions; thal, thalamus; TPN, Total Parenteral Nutrition; VSS, Viking Speech Scale; Y, years.

^a Early = age ≤ 6 weeks, late = age > 6 weeks.

Table 2 shows the association between MRI findings and NDO. In the total group the positive predictive value (PPV) of an abnormal MRI for an impaired NDO was 77.5 %. The negative predictive value (NPV) of a normal MRI for a normal NDO was much lower with 29.0 %.

A subanalysis for prematurity was performed. The sample sizes were small in this analysis; a total of 21 pre-term infants and 96 term infants. In three patients gestational age was not mentioned, they were not included in this analysis. In case of an abnormal MRI in pre-term infants, 14 out of 17 patients had an impaired NDO, with a PPV of 82.4 %. In case of an abnormal MRI in term infants, 53 out of 70 had an impaired NDO, with a PPV of 75.7 %. The NPV of a normal MRI and a normal outcome for pre-term and term infants was 25 % and 30.8 %, respectively.

Subsequently, in the total group (n = 120) we performed a second subanalysis investigating the association between abnormal MRI findings and specific outcome domains (motor impairment, auditory impairment, and cognitive impairment), see Table 2.

Since not all studies reported outcome in every specific domain, patient numbers per domain varied for these subanalyses. Motor impairment was present in 65.8 % (52 of 79) of the infants, auditory impairment in 57.0 % (45 of 79) of the infants and cognitive impairment in 21.2 % (7 of 33) of the infants. The PPVs of the MRI for impaired NDO in the motor, auditory and cognitive domains were 73.2 %, 60.7 % and 27.8 % respectively. The NPVs of MRI for a normal outcome in the motor, auditory and cognitive domain were 52.2 %, 52.2 % and 86.7 % respectively. Of the seven patients who died, five had an abnormal MRI (four early (of which two also had a second late abnormal MRI) and one timing not mentioned). Two of these seven patients had a normal MRI.

Table 3 demonstrates the association between the timing of MRI and the NDO. Cases of whom the timing of MRI was not mentioned (n = 26) were not included in this analysis. Early MRI was performed for 75 patients (range five days/first week – six weeks). A median age could not be calculated for this group due to the fact that descriptions of timing ranged from ‘neonatal’ (n = 29) to ‘first week’ (n = 5) to ‘10–20 days’ (n = 1) to a specific amount of days (n = 40), with a median age in these 40 patients of 12 days (range 5 days–6 weeks). Late MRI was performed for 19 patients, yielding a median age of 11.4 months (range 2–24 months). In case of an early abnormal MRI, 38 out of 53 patients had impairments at follow-up, with a PPV of 71.7 %. However, in the case of a late abnormal MRI, 12 out of 13 patients had an impaired NDO, with a PPV of 92.3 %. The NPV of a normal MRI is much lower for both early and late MRIs; again it is greater for late MRI than for early MRI (50.0 % and 27.3 % respectively), with small sample sizes here as well.

The three studies [34–36] that presented patient data combined as a group are described here.

Van Toorn et al. [34] studied a group of 30 children (mean age of follow-up 71 months) exposed to hazardous hyperbilirubinemia during the first days of postnatal life with signs and symptoms suggestive of ABE; 25 children (83 %) underwent MRI at a mean age of 6.5 months (range 0.23–22.79 months). Pallidal hyperintensity was observed on T1-weighted images in the acute phase and on T2-weighted images in the chronic phase in the majority of the children. They found that children with normal MRI findings were more likely to have a milder degree of motor impairment (defined as: high functioning, little to no functional disability, possible learning disabilities, subtle movement disorders, and occasional muscle cramps).

Yuan et al. [35] described a group of 77 neonates in which the predictive value of early amplitude integrated electroencephalography (aEEG) was compared to that of MRI and the auditory brainstem response (ABR). Clinical follow-up was till the age of 12 months. Seventy-one of those neonates had severe hyperbilirubinemia. In the total group, only 40 MRI scans were performed (within 24 h after the bilirubin level had normalized). They reported that 22 out of 29 infants (75.9 %) with a favorable outcome had a normal MRI, and 5 out of 11 infants (45.5 %) with an impaired outcome had an abnormal MRI (hyperintense signal in the globus pallidus on T1 weighted imaging). Yuan et al. [35] also studied the predictive value of ABR. In this study,

Table 2
Relation between MRI and impaired Neurodevelopmental Outcome.

MRI abnormal	Total NDO			Motor Outcome			Auditory Outcome			Cognitive Outcome		
	Impaired, n (%)	Normal, n (%)	Total, n (%)	Impaired, n (%)	Normal, n (%)	Total, n (%)	Impaired, n (%)	Normal, n (%)	Total, n (%)	Impaired, n (%)	Normal, n (%)	Total, n (%)
Yes	69 (57.5 %)	20 (16.7 %)	89 (74.2 %)	41 (51.9 %)	15 (19.0 %)	56 (70.9 %)	34 (43.0 %)	22 (27.8 %)	56 (70.9 %)	5 (15.2 %)	13 (39.4 %)	18 (54.5 %)
No	22 (18.3 %)	9 (7.5 %)	31 (25.8 %)	11 (13.9 %)	12 (15.2 %)	23 (29.1 %)	11 (13.9 %)	12 (15.2 %)	23 (29.1 %)	2 (6.1 %)	13 (39.4 %)	15 (45.5 %)
Total	91 (75.8 %)	29 (24.2 %)	120 (100 %)	52 (65.8 %)	27 (34.2 %)	79 (100 %)	45 (57.0 %)	34 (43.0 %)	79 (100 %)	7 (21.2 %)	26 (78.8 %)	33 (100 %)

Abbreviations: NDO, Neurodevelopmental Outcome.

Table 3
Relation of timing of MRI and Neurodevelopmental Outcome.

Timing of MRI		Total NDO		
		Impaired, n (%)	Normal, n (%)	Total, n (%)
Early ^a	MRI abnormal	38 (50.7 %)	15 (20.0 %)	53 (70.7 %)
	MRI normal	16 (21.3 %)	6 (8.0 %)	22 (29.3 %)
	Total	54 (72.0 %)	21 (28.0 %)	75 (100 %)
Late ^b	MRI abnormal	12 (63.2 %)	1 (5.3 %)	13 (68.4 %)
	MRI normal	3 (15.8 %)	3 (15.8 %)	6 (31.6 %)
	Total	15 (78.9 %)	4 (21.1 %)	19 (100 %)

Abbreviations: NDO, Neurodevelopmental Outcome.

^a (age ≤6 weeks).

^b (age >6 weeks).

the PPV of an abnormal ABR for an abnormal NDO was 58.8 % and the NPV of a normal ABR for a normal outcome was 90.9 %.

Mukhopadhyay et al. [36] described a group of 25 neonates suffering from severe hyperbilirubinemia and clinical signs of intermediate to advanced ABE. Fifteen infants completed follow-up at one year of age. MRIs were performed in 18 patients (pre- or soon after discharge), and 11 of them showed symmetrical hyperintensity in the globus pallidus on T1-weighted imaging. They reported that five of the 11 neonates with abnormal MRI data had a normal NDO and that one infant with a normal MRI had an impaired NDO at the 1-year follow-up. The study concluded that an abnormal MRI was not associated with an abnormal outcome.

Eight studies [19,20,24,28–30,32,33] described MRI abnormalities (abnormal MRI n = 32) in more detail. Of these 32 patients, 22 (68.8 %)

Table 4
Serial MRI scans.

Patient	First MRI (age)	Result first MRI	Second MRI (age)	Result second MRI	Third MRI (age)	Result third MRI	Outcome (age)
1 ¹⁹	Early (9d)	Normal	Late (9m)	Normal	–	–	Normal (6y)
2 ¹⁹	Early (9d)	Abnormal	Late (10m)	Normal	–	–	Impaired (5y)
3–12 ^{23,24,32,33}	8 Early (12d-neonatal), 2 late (7m + 24m)	Abnormal	Late (3m-13y)	Abnormal	–	–	Impaired (1-13y)
13–16 ^{24,33}	Early (5d-5w)	Abnormal	Late (3–22m)	Normal	–	–	Normal (1-3.5y)
17 ²⁴	Early (7d)	Normal	Late (3m)	Normal	Late (6m)	Abnormal	Impaired (1.8y)
18–21 ²⁴	Early (2w-neonatal)	Abnormal	1 Early (6w), 2 Late (3m)	Abnormal	Late (12–13m)	Abnormal	Impaired (1-1.8y)
22 ²⁷	Early (between 10 and 20d)	Normal	Late (12m)	Abnormal	–	–	Impaired (13y)
23+24 ³²	1 Early (neonatal), 1 Late (2m)	Normal	Late (3m+9m)	Abnormal	Late (12m + 34m)	Abnormal	Impaired (6y)
25 ³³	Early (neonatal)	Normal	Late (3m)	Normal	–	–	Impaired (1y)
26 ³³	Late (3m)	Abnormal	Late (12m)	Abnormal	–	–	Normal (1y)
27+28 ³³	Early (neonatal)	Abnormal	Late (3m)	Normal	Late (12m)	Abnormal	Normal (1y)
29 ³³	Early (neonatal)	Normal	Late (3m)	Normal	Late (12m)	Normal	Normal (1y)
30 ³³	Early (neonatal)	Abnormal	Late (3m)	Abnormal	Late (12m)	Abnormal	Normal (1y)
31 ³³	Early (neonatal)	Abnormal	Late (3m)	Normal	Late (12m)	Normal	Normal (1y)

Abbreviations: d, days; m, months; w, weeks; y, years.

had early MRI scans. In those early MRI patients T1-weighted hyperintensity of mainly the globus pallidus and subthalamic nucleus was described. Three patients with an early MRI had a slightly hyperintense T2 weighted signal of the globus pallidus as well. In two of them additionally, a hypointense T2-weighted signal in the subthalamic nucleus was found.

Of the 10 patients (31.3 %) who had a late MRI, the main finding was a hyperintense T2-weighted signal in the globus pallidus in all patients. In addition, in two of them a T1-weighted hypointense signal in the globus pallidus was found.

Only six studies described longitudinal MRI scans. Nineteen patients underwent two serial MRIs, and two patients underwent twelve serial MRI scans. The MRI and outcome results can be found in Table 4.

4. Discussion

In this systematic review, we investigated the association between MRI findings in both pre-term and term infants with severe unconjugated hyperbilirubinemia (above exchange transfusion levels) and their NDO at a minimum (corrected) age of 12 months. To our knowledge, this is the first comprehensive synthesis on this subject. Our main findings include a high PPV of abnormal brain MRI, (77.5 %) for impaired NDO, but a low NPV of a normal brain MRI for a normal NDO (29 %), showing that there is still quite a high chance of having an impaired follow-up despite a normal MRI scan. Among our patients 75.8 % had an impaired NDO, which is significantly higher than the 5.7%–18.2 % reported in other studies [9,37]. The definition of severe hyperbilirubinemia between those studies differed between >428 μmol/L and >513 μmol/L. Compared to this literature, the high number of patients with an impaired outcome in this review cannot be fully representative of all patients with severe unconjugated

hyperbilirubinemia. There appears to have been a selection bias toward the inclusion of patients with an impaired outcome in the studies included in this review. Also, the high number may be due to our wide NDO range, from truncal hypotonia with stereotypes to dyskinetic or tetraplegic cerebral palsy. In contrast, other studies with lower numbers of impaired NDO might have limited themselves to only a serious outcome.

The prognostic value of MRI timing was also highlighted. Late MRI had a clearly higher PPV (92.3 %) than early MRI (71.7 %), but the small sample size (n = 19 for late MRI) and the lack of direct comparisons between early and late MRI in the same population limit these findings. Notably, ten out of 31 patients with serial MRIs (Table 4), showed MRI changes from normal to abnormal or vice versa at follow-up. One of the explanations could be that physiological myelination, reflected as high T1-weighted intensity due to the high lipid content of myelin, of the globus pallidus and subthalamic nucleus might be falsely interpreted as abnormal on early MRI [10]. In our review, we used six weeks as a cutoff point for early versus late MRI; we realize that with regard to the late group, this still encompasses a wide age range.

Detailed information on MRI abnormalities was limited to only eight out of 22 studies. These studies generally confirmed the typical shift from T1-weighted hyperintensity in the acute phase to T2-weighted hyperintensity in the chronic phase, reflecting gliosis, as described in previous literature [11–15].

Currently, there is no consensus on the optimal timing for MRI. Govaert et al. [12] suggested that T1-weighted signal loss occurs between the first and third weeks, while T2-weighted hyperintensity can appear as early as day 18 [38]. Gkoltsiou et al. [24] reported that the reaction to bilirubin neurotoxicity in extremely premature brains might be lengthy due to a decreased metabolic rate in pre-term neonates compared with term neonates. They suggested a post-term age of at least five months when performing an MRI scan.

Another aspect that should be taken into account with regard to the early MRI, is the logistical fact that an MRI is not always available and/or not possible in every center in very young infants. In addition, the decision to perform an MRI should weigh its high cost and the fact that, despite providing predictive information, uncertainties about the prognosis may still remain.

It is known that pre-term neonates are more susceptible to intracerebral damage at lower bilirubin levels [39]. Furthermore, pre-term birth may be associated with abnormal NDO, even without kernicterus. Although our subanalysis did not reveal significant differences in predictive values between term and pre-term neonates, the lack of detailed gestational age data precluded a thorough examination of prematurity’s impact. Despite our earlier described exclusion criteria, it cannot be ruled out that in a NICU population, with severely ill patients, there could have been other factors that might have influenced their NDO.

The heterogeneity in study design, including varied populations, MRI timing and outcome measures, prevented a quantitative synthesis

of results. The binary classification of MRI outcome is simplistic and could affect the interpretation of results and parental counseling.

High-quality studies linking MRI abnormalities at various time points to NDO are lacking, making it difficult to formulate unambiguous evidence-based advice for performing MRI in this population. Both early and late MRIs have their limitations, as summarized in Fig. 3, and clinical practice should consider these. For early MRI, we suggest performing it within the first to third week, due to the described shift from a hyperintense T1 to T2 signal after this period [38]. Practical considerations, such as the need for sedation at older ages, can also play a role in the preferred timing for MRI in individual cases.

We focused on T1- and T2-weighted MRI sequences, commonly used for diagnosing KSD. The predictive value of (neonatal) ABR was not investigated, though previous studies indicate ABR can be another tool to predict KSD. Only two studies [33,35] included in this review compared the predictive value of ABR versus MRI in one study.

Yuan et al. [35] revealed that ABR performed in the acute phase is a better predictor for KSD than MRI. However, Gelineau et al. [33] state that an ABR indicative of auditory neuropathy spectrum disorder in the neonatal period does not predict KSD.

Recent studies have explored other imaging techniques in KSD [34–36]. Cece et al. [40] and Wang et al. [25] reported higher apparent diffusion coefficient (ADC) values in infants with kernicterus using diffusion-weighted imaging (DWI). A recent prospective cohort study [41] using functional MRI (fMRI) and amplitude of low frequency fluctuations (ALFF) data, showed that the ALFF value in the basal ganglia was highest in infants with severe hyperbilirubinemia and was correlated with neurodevelopmental outcome. Further investigation into the significance of these promising new imaging techniques could shed light on their utility as predictive biomarkers of NDO in this population.

Despite summarizing 22 studies, our review does not provide unambiguous evidence-based conclusions, highlighting the need for further research on this subject. We recommend performing a large, prospective, longitudinal study with regular imaging intervals (for instance in the acute phase, at 3 months (without sedation) and after 2 years of age when myelination has been completed), including T1- and T2-weighted sequences and advanced techniques such as susceptibility-weighted imaging (SWI), DWI, magnetic resonance spectroscopy (MRS) or fMRI. Risk factors such as the highest unconjugated bilirubin level, the need for exchange transfusion, bilirubin-induced neurological dysfunction (BIND) scores and/or the results of an ABR should be included. Clinical follow-up should be uniform (including a neonatal general movements assessment and a general movements assessment at 3 months) and cover multiple domains. Separate analyses for pre-term and term infants are essential. Artificial Intelligence could help by making a predictive algorithm based on the risk factors and clinical outcome. Multicenter collaboration would be necessary due to the rarity of bilirubin-induced brain injury.

Early MRI scan (age ≤ 6 weeks) Preferably between week 0-3	Late MRI scan (age > 6 weeks)
T1-weighted hyperintensity	T2-weighted hyperintensity
Positive predictive value +	Positive predictive value +++
Negative predictive value -	Negative predictive value +/-
Ease of scan +	Ease of scan (often sedation required) -
Early first impression ++	Early first impression +
False positive due to transient damage/edema or physiological myelination	False positive less common

Fig. 3. Early versus late MRI, clinical features.

5. Conclusion

In neonates with severe unconjugated hyperbilirubinemia, MRI brain scans at both the early and late stages may serve as a prognostic tool for long-term neurodevelopmental outcomes. However, each timing has inherent constraints, such as potential misinterpretation of early physiological changes and the logistical challenges of late imaging. Further prospective studies are needed to establish optimal imaging protocols and to enhance predictive accuracy.

Funding/support

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Declaration of competing interest

None.

Appendix A. Search strategy

For PubMed the following search strategy was used: ("Hyperbilirubinemia"[MeSH Terms] OR hyperbilirubine*[Title/Abstract] OR hyper bilirubinemia[Title/Abstract] OR hyperbilirubinaemia[Title/Abstract] OR bilirubinem*[Title/Abstract] OR bilirubin encephalopathy [Title/Abstract] OR kernicterus[Title/Abstract] OR bilirubin induced neurologic dysfunction[Title/Abstract] OR BIND[Title/Abstract] OR jaundice*[Title/Abstract] OR icterus[Title/Abstract] OR bilirubin toxicit*[Title/Abstract]) AND ("Infant"[MeSH Terms] OR infant*[Title/Abstract] OR premature*[Title/Abstract] OR newborn*[Title/Abstract] OR neonate*[Title/Abstract] OR baby[Title/Abstract] OR babies[Title/Abstract]) AND ("Magnetic Resonance Imaging"[MeSH Terms] OR MRI [Title/Abstract] OR tomograph*[Title/Abstract] OR magnetic resonance imag*[Title/Abstract] OR MR[Title/Abstract] OR NMR[Title/Abstract]).

For Embase the following search strategy was used: ('neonatal hyperbilirubinemia'/exp OR 'hyperbilirubine*':ti,ab,kw OR 'hyper bilirubinemia':ti,ab,kw OR 'hyperbilirubinaemia':ti,ab,kw OR 'bilirubinem*':ti,ab,kw OR 'bilirubin encephalopathy':ti,ab,kw OR 'kernicterus':ti,ab,kw OR 'bilirubin induced neurologic dysfunction':ti,ab,kw OR 'bind':ti,ab,kw OR 'jaundice':ti,ab,kw OR 'icterus':ti,ab,kw OR 'bilirubin toxicit*':ti,ab,kw) AND ('infant'/exp OR 'infant*':ti,ab,kw OR 'premature*':ti,ab,kw OR 'newborn*':ti,ab,kw OR 'neonate*':ti,ab,kw OR 'baby':ti,ab,kw OR 'babies':ti,ab,kw) AND ('magnetic resonance imaging':ti,ab,kw OR 'mri':ti,ab,kw OR 'tomography':ti,ab,kw OR 'mr':ti,ab,kw OR 'nmr':ti,ab,kw).

References

- [1] T. Hegyi, A. Kleinfeld, Neonatal hyperbilirubinemia and the role of unbound bilirubin, *J Matern Neonatal Med* 35 (25) (2022) 9201–9207.
- [2] S. Das, F.K.H. van Landeghem, Clinicopathological spectrum of bilirubin encephalopathy/kernicterus, *Diagnostics* 9 (1) (2019) 1–12.
- [3] F. Usman, U. Diala, S. Shapiro, J.-B. Le Pichon, T. Slusher, Acute bilirubin encephalopathy and its progression to kernicterus: current perspectives, *Res Reports Neonatol* 8 (2018) 33–44.
- [4] A. Riskin, A. Tamir, A. Kugelman, M. Hemo, D. Bader, Is visual assessment of jaundice reliable as a screening tool to detect significant neonatal hyperbilirubinemia? *J. Pediatr.* 152 (6) (2008).
- [5] S. Shapiro, J.B. Le Pichon, S.M. Riordan, J. Watchkoe, The neurological sequelae of neonatal hyperbilirubinemia: definitions, diagnosis and treatment of the kernicterus spectrum disorders (KSDs), *Curr. Pediatr. Rev.* 13 (2017) 199–209.
- [6] S.M. Shapiro, H. Nakamura, Bilirubin and the auditory system, *J. Perinatol.* 21 (2001) S52–S55.
- [7] M. Sgro, D.M. Campbell, S. Kandasamy, V. Shah, Incidence of chronic bilirubin encephalopathy in Canada, 2007–2008, *Pediatrics* 130 (4) (2012) e886–e890.
- [8] M.L. Donneborg, B.M. Hansen, P.K. Vandborg, M. Rodrigo-Domingo, F. Ebbesen, Extreme neonatal hyperbilirubinemia and kernicterus spectrum disorder in Denmark during the years 2000–2015, *J Perinatol Off J Calif Perinat Assoc* 40 (2) (2020 Feb) 194–202.
- [9] M.W. Kuzniewicz, A.C. Wickremasinghe, Y.W. Wu, C.E. McCulloch, E.M. Walsh, S. Wi, et al., Incidence, etiology, and outcomes of hazardous hyperbilirubinemia in newborns, *Pediatrics* 134 (3) (2014) 504–509.
- [10] J.L. Wisnowski, A. Panigrahy, M.J. Painter, J.F. Watchko, Magnetic resonance imaging of bilirubin encephalopathy: current limitations and future promise, *Semin. Perinatol.* 38 (7) (2014) 422–428.
- [11] A. Coskun, A. Yikilmaz, S. Kumandas, O.I. Karahan, M. Akcakus, A. Manav, Hyperintense globus pallidus on T1-weighted MR imaging in acute kernicterus: is it common or rare? *Eur. Radiol.* 15 (6) (2005 Jun) 1263–1267.
- [12] P. Govaert, M. Lequin, R. Swarte, S. Robben, R. De Co, N. Weisglas-Kuperus, et al., Changes in globus pallidus with (Pre)Term kernicterus, *Pediatrics* 112 (6) (2003 Dec) 1256–1263.
- [13] S.M. Shapiro, Chronic bilirubin encephalopathy: diagnosis and outcome, *Semin. Fetal Neonatal Med.* 15 (3) (2010 Jun) 157–163.
- [14] M. Steinborn, K.C. Seelos, A. Heuck, H. Von Voss, M. Reiser, MR findings in a patient with Kernicterus, *Eur. Radiol.* 9 (9) (1999) 1913–1915.
- [15] S. Sugama, A. Soeda, Y. Eto, Magnetic resonance imaging in three children with kernicterus, *Pediatr. Neurol.* 25 (4) (2001) 328–331.
- [16] M. Ouzzani, H. Hammady, Z. Fedorowicz, A. Elmagarmid, Rayyan-a web and mobile app for systematic reviews, *Syst. Rev.* 5 (1) (2016) 1–10.
- [17] W.K. Oakden, A.M. Moore, S. Blaser, M.D. Noseworthy, 1H MR spectroscopic characteristics of kernicterus: a possible metabolic signature, *Am. J. Neuroradiol.* 26 (6) (2005) 1571–1574.
- [18] F. Groenendaal, J. van der Grond, L.S. de Vries, Cerebral metabolism in severe neonatal hyperbilirubinemia, *Pediatrics* 114 (1) (2004 Jul) 291–294.
- [19] M.C. Harris, J.C. Bernbaum, J.R. Polin, R. Zimmerman, R.A. Polin, Developmental follow-up of breastfed term and near-term infants with marked hyperbilirubinemia, *Pediatrics* 107 (5) (2001) 1075–1080.
- [20] Y. Yilmaz, G. Alper, G. Kilicoglu, L. Celik, L. Karadeniz, S. Yilmaz-Degirmenci, et al., Magnetic resonance imaging findings in patients with severe neonatal indirect hyperbilirubinemia, *J. Child Neurol.* 16 (6) (2001 Jun) 452–455.
- [21] A. Nickisch, C. Massinger, B. Ertl-Wagner, H. von Voss, Pedaudiologic findings after severe neonatal hyperbilirubinemia, *Eur. Arch. Oto-Rhino-Laryngol.* 266 (2) (2009 Feb) 207–212.
- [22] T.W.R. Hansen, L. Nietsch, E. Norman, J.V. Bjerre, J.-M. Hascoet, K. Mreihil, et al., Reversibility of acute intermediate phase bilirubin encephalopathy, *Acta Paediatr Int J Paediatr* 98 (10) (2009 Oct) 1689–1694.
- [23] Y.W. Wu, M.W. Kuzniewicz, A.C. Wickremasinghe, E.M. Walsh, S. Wi, C. E. McCulloch, et al., Risk for cerebral palsy in infants with total serum bilirubin levels at or above the exchange transfusion threshold: a population-based study, *JAMA Pediatr.* 169 (3) (2015 Mar) 239–246.
- [24] K. Gkoltsiou, M. Tzoufi, S. Counsell, M. Rutherford, F. Cowan, Serial brain MRI and ultrasound findings: relation to gestational age, bilirubin level, neonatal neurologic status and neurodevelopmental outcome in infants at risk of kernicterus, *Early Hum. Dev.* 84 (12) (2008 Dec) 829–838.
- [25] X. Wang, W. Wu, B.L. Hou, P. Zhang, A. Chineah, F. Liu, et al., Studying neonatal bilirubin encephalopathy with conventional MRI, MRS, and DWI, *Neuroradiology* 50 (10) (2008 Oct) 885–893.
- [26] W. Wu, P. Zhang, X. Wang, A. Chineah, M. Lou, Usefulness of (1) H-MRS in differentiating bilirubin encephalopathy from severe hyperbilirubinemia in neonates, *J Magn Reson Imaging* 38 (3) (2013 Sep) 634–640.
- [27] S.L. Merhar, D.L. Gilbert, Clinical (video) findings and cerebrospinal fluid neurotransmitters in 2 children with severe chronic bilirubin encephalopathy, including a former preterm infant without marked hyperbilirubinemia VIDEO, *Pediatrics* 116 (5) (2005 Nov) 1226–1230.
- [28] M.H. Atalar, D. Buyakayhan, D. Icaogiosoglu, Magnetic resonance imaging of the brain in children with chronic kernicterus, *Neurosciences* 11 (3) (2006) 201–204.
- [29] Y. Yilmaz, G. Ekinci, Thalamic involvement in a patient with kernicterus, *Eur. Radiol.* 12 (7) (2002 Jul) 1837–1839.
- [30] U.C. Parashari, R. Singh, R. Yadav, P. Aga, Changes in the globus pallidus in chronic kernicterus, *J. Pediatr. Neurosci.* 4 (2) (2009) 117–119.
- [31] S. Abe, K. Fujioka, Can exchange transfusion be replaced by double-LED phototherapy? *Open Med.* 16 (1) (2021) 992–996.
- [32] J. Gburek-Augustat, I. Sorge, M. Stange, J. Kern, A. Merckenschlager, T. Nägele, et al., Acute and chronic kernicterus: MR imaging evolution of globus pallidus signal change during childhood, *AJNR Am J Neuroradiol* 44 (9) (2023 Sep) 1090–1095.
- [33] R. Gelineau-Morel, F. Usman, S. Shehu, H.W. Yeh, M.A. Suwaid, M. Abdulsalam, et al., Predictive and diagnostic measures for kernicterus spectrum disorder: a prospective cohort study, *Pediatr. Res.* 95 (1) (2024) 285–292.
- [34] R. van Toorn, P. Brink, J. Smith, C. Ackermann, R. Solomons, Bilirubin-induced neurological dysfunction: a clinico-radiological-neurophysiological correlation in 30 consecutive children, *J. Child Neurol.* 31 (14) (2016 Dec) 1579–1583.
- [35] X. Yuan, J. Song, L. Gao, Y. Cheng, H. Dong, R. Zhang, et al., Early amplitude-integrated electroencephalography predicts long-term outcomes in term and near-term newborns with severe hyperbilirubinemia, *Pediatr. Neurol.* 98 (2019 Sep) 68–73.
- [36] K. Mukhopadhyay, G. Chowdhary, P. Singh, P. Kumar, A. Narang, Neurodevelopmental outcome of acute bilirubin encephalopathy, *J. Trop. Pediatr.* 56 (5) (2010) 333–336.
- [37] V.K. Bhutani, L. Johnson, Kernicterus in the 21st century: frequently asked questions, *J. Perinatol.* 29 (2009) S20–S24.
- [38] V. Martich-Kriss, S.S. Kollias, W.S.J. Ball, MR findings in kernicterus, *Am. J. Neuroradiol.* 16 (SUPPL) (1995 Apr) 819–821.

- [39] V. Bhutani, R. Wong, Bilirubin neurotoxicity in preterm infants: risk and prevention, *J Clin Neonatol* 2 (2) (2013) 61.
- [40] H. Cece, M. Abuhandan, A. Cakmak, S. Yildiz, M. Calik, E. Karakas, et al., Diffusion-weighted imaging of patients with neonatal bilirubin encephalopathy, *Jpn. J. Radiol.* 31 (3) (2013 Mar) 179–185.
- [41] K. Yan, F. Xiao, Y. Jiang, C. Lu, Y. Zhang, Y. Kong, et al., Amplitude of low-frequency fluctuation may be an early predictor of delayed motor development due to neonatal hyperbilirubinemia: a fMRI study, *Transl. Pediatr.* 10 (5) (2021 May) 1271–1284.