REVIEW

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Neuropsychomotor development in children and adolescents with liver diseases: systematic review with meta-analysis

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ABSTRACT – **Background** – The nature of liver disease, the evolutionary course and duration of liver diseases, as well as the degree of severity and disability can trigger multiple outcomes with repercussions on neuromotor acquisition and development. **Objective** – To systematically review and conduct a meta-analysis to evaluate the effects of liver disease on the neuropsychomotor development of children and adolescents with their native livers and those who underwent liver transplantation. **Methods** – Observational studies published since the early 1980s until June 2019 were sought in the PubMed and Scopus databases. An α value of 0.05 was considered significant. The statistical heterogeneity of the treatment effect between the studies was assessed by the Cochran's Q test and the I2 inconsistency test, in which values above 25 and 50% were considered indicative of moderate and high heterogeneity, respectively. Analyses were performed with Review Manager 5.3. **Results** – Twenty-five studies met the eligibility criteria, including 909 children and adolescents with liver disease. Meta-analyses showed deficits in total IQ -0.41 (95%CI: -0.51 to -0.32; N: 9,973), verbal IQ -0.38 (95%CI: -0.57 to -0.18; N: 10,284) and receptive language -0.85 (95%CI: -1.16 to -0.53; N: 921) in liver transplantation, and those with native livers who had symptoms early had total and verbal IQ scores (85±8.8; 86.3±10.6 respectively) lower than the scores of those with late manifestations (99.5±13.8; 96.2±9.2). Gross motor skill was reduced -46.29 (95%CI: -81.55 to -11.03; N: 3,746). **Conclusion** – Acute or chronic liver disease can cause declines in cognitive, motor and language functions. Although the scores improve after liver transplantation, children remain below average when compared to healthy children.

Keywords – Liver disease; liver transplantation; child development.

INTRODUCTION

Childhood liver diseases may be diagnosed at a late moment or even be underdiagnosed by pediatricians due to their asymptomatic character or nonspecific signs and symptoms in the initial phase[1], acute manifestation or progression to chronicity, with onset or persistence of changes in biochemical and/or laboratory tests[1,2]. In Brazil, there are about 61.2 million children[2], and the number of children needing liver transplantation (LT) to survive grows every year. In recent years, an average of 204 liver transplants have been performed per year, with a survival rate greater than 90% in the first year after this procedure[3].

With the increase in life expectancy after treatment of liver diseases, it is observed that the focus of professionals who deal with these children has expanded from mere survival to a careful look at long-term functionality and quality of life[4]. Neuropsychomotor aspects, such as cognitive function, and motor and social development are essential skills for the adequate school development and future occupational activity of these children and adolescents and also for family balance[5].

Some studies have shown cognitive deficits in attention, intelligence, motor and language deficits in patients with liver diseases[5-8]. The earlier the brain is exposed to neurotoxic disease conditions, the greater the neuropsychomotor damage. On the other hand, the shorter the time between indication and transplantation, the less damage to the immature neurological system and the greater the chances of recovery due to neuroplasticity in young patients[5]. However, little is known about the motor development of children who remain with their native liver[6].

In 2018, Rodijk et al.[6] carried out a systematic review with the objective of determining neurodevelopmental results in children with liver disease, but without meta-analysis. To our knowledge, no meta-analysis compiling data on neuropsychomotor development involving children and adolescents with acute and chronic liver diseases has been published so far. Thus, the aim of this study was to systematically review the effects of liver disease on the neuropsychomotor development of children and adolescents with their native livers and of those who underwent LT, and compare the results of cognitive, language and motor skills between these two groups through a meta-analysis.

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METHODS

Systematic review and meta-analysis carried out according to PRISMA recommendations and guidelines.

Selection criteria

Nineteen cross-sectional and six longitudinal studies that investigated aspects of neuropsychomotor (neurocognitive and neuromotor) development of children and adolescents with acute and chronic liver diseases were included in the study. The results of interest were: intelligence coefficients (full and verbal IQ), perceptual reasoning, working memory, processing speed, general, receptive and expressive language, general motor skill, manual dexterity, ability with a ball and balance. Articles in which the age of the participants was ≥18 years and which presented other diseases in addition to liver diseases were excluded.

Search strategy

Searches were performed in the databases PubMed and Scopus databases, including the first studies published in the 1980s until June 2019, without restrictions of language or publication status. The search was carried out by two independent reviewers, who read the titles and abstracts. A third reviewer read the articles in full length and applied the inclusion and exclusion criteria for selection of manuscripts. The references of the included articles were revised to identify potential studies. The following Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCS) in the English language were used as keywords: "liver diseases in children", "developmental disorders", "neuropsychomotor delays", "cognitive delays", "child liver transplantation", "learning disorders", "motor delays", "chronic liver failure" and "observational studies", with combinations made using "AND" and/or "OR".

Assessment of methodological quality

The Newcastle-Ottawa scale (NOS) for quality assessment was used to evaluate the risks of bias in the included studies[7]. Ten stars were adopted for cross-sectional studies. A maximum of six stars was assigned to cohort studies, since none of the included studies selected an unexposed cohort and no comparison could be made. Adequate follow-up was defined as that conducted for at least 12 months.

Statistical analysis

Estimates of the combined effect were obtained by comparing the minimum squares of the average percentage variation between measures obtained for each group, and were expressed as weighted average differences between groups. The calculations were made using a random effects model. Two comparisons were made: Post-liver transplant group versus control group and Pre-liver transplant group versus control group. Reference values for standardization of the scales that evaluated the variables in each study were used to perform the meta-analysis of studies that did not have a control group[9-12].

An α value of 0.05 was considered significant. The statistical heterogeneity of the treatment effect between studies was assessed by the Cochran Q test and the inconsistency index test, where values above 25 and 50% were considered to indicate moderate and high heterogeneity, respectively. If meta-analysis was not possible due to clinical heterogeneity, data were analyzed descriptively. All analyses were performed using Review Manager version 5.0 (Cochrane Collaboration)[13].

RESULTS

Description of selected studies

Initially, 8,124 related articles were identified. After reading the titles and abstracts, the two independent reviewers selected 72 articles, which were considered potentially relevant. A third reviewer read the studies in full length and applied the inclusion and exclusion criteria, and a total of 25 articles were selected (FIGURE 1). The number of participants with liver diseases was 909, and 649 underwent LT. The period of publication of the studies was from 1988 to 2018; the size of the population with liver diseases studied in the articles varied between 13[14] to 144[9], and the average age of the participants ranged from 3[10] months to 18 years[11]. Results of the assessment of risk of bias are presented in FIGURE 2.

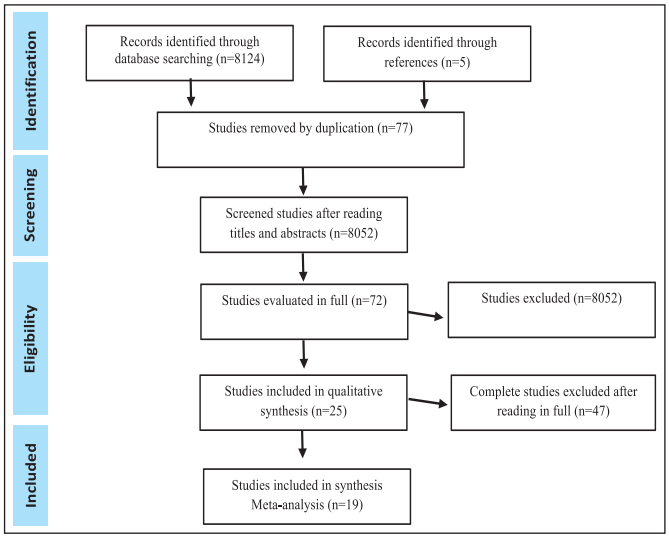

FIGURE 1. Flow diagram of studies for inclusion in the systematic review.

Cross-sectional	Selection	Comparability	Outcome	Study quality
Lee et al., 2017	***	*	***	7/10
Kaller et al., 2013	****	**	***	9/10
Sorensen et al., 2015	****	**	***	9/10
Sorensen et al., 2011	****	*	***	8/10
Sorensen et al., 2014	****	**	***	9/10
Afshar et al., 2018	****	**	***	9/10
Macedo et al., 2017	****	**	***	9/10
Almaas et al., 2015	****	**	***	9/10
Ee et al., 2014	*****	**	***	10/10
Haavisto et al., 2011	****	**	***	9/10
Caudle et al., 2012	****	**	***	9/10
Caudle et al., 2010	****	**	***	9/10
Abu Faddan et al., 2014	***	*	***	7/10
Krull et al., 2003	****	*	***	8/10
Rodrigue et al., 2009	****	*	***	8/10
Gold et al., 2017	****	*	***	8/10
Stewart et al., 1991	***	*	***	7/10
Kaller et al., 2010	***	**	***	8/10
Stewart et al., 1988	***	**	***	8/10
Cohort	**Selection**	**Comparability**	**Outcome**	**Total**
Sorensen et al., 2018	**	=	***	5/6
Gilmour et al., 2009	**	=	***	5 /6
NG et al., 2018	**	=	***	5/6
Wayman et al., 1997	**	=	**	4/6
van Mourik et al., 2000	**	=	**	4/6
Stewart et al., 1989	**	=	***	5/6

FIGURE 2. Quality assessment of included studies.

Study characteristics

All studies investigated some aspect of neuropsychomotor development in children and adolescents with acute and/or chronic liver diseases. Nineteen studies were conducted with children after LT. The most common diseases were biliary atresia, cholestatic diseases, and diseases of metabolic and viral etiologies. Eight studies had a control group. Nineteen studies were subject to meta-analysis.

Ten instruments were used to evaluate the variables of interest. For cognition and executive functions, versions of the Wechsler Intelligence Scales (WISC) were the most used (15/17)[5,9,12,14-22]. General, fine and gross motor development were assessed using the following instruments: Movement Assessment Battery for Children (M-ABC)[23], Mullen Scales of Early Learning (MSEL)[10,24], Bayley Development Scales[25,26], Griffiths Mental Ability Scales (GMDS)[27] and General Development Scale of Minnesota Child Development Inventory (MCDI)[15]. Some of these instruments also evaluated general language[25], receptive and expressive language[10,24] (TABLE 1).

TABLE 1. Characterization of studies on neuropsychomotor development in children and adolescents with liver disease.

Authors / year	Study design	Participants / age range	Liver disease	Assessment	Neurognitive results
Lee et al., 2017	Cross-sectional	28 (0.5–15.3 years)	Chronic (LT)/BA	WPPSI-III	= FSIQ, VIQ
Kaller et al., 2013	Cross-sectional	64/64 (6–16 years)	Chronic (LT) /BA, CD, MGD	WISC-IV	↓ FSIQ, VIQ, PRI, WMI, PSI
Sorensen et al., 2015	Cross-sectional	36/ (6–16 years)	Acute (LT)/ AT, AD, MD, VI, IN, OT	WISC-IV	= FSIQ, VIQ, PRI, WMI, PSI
Sorensen et al., 2018	Longitudinal	25/ (<18 years)	Acute (LT)/AT, AD, MD, VI, IN, OT	WISC-IV	= FSIQ, VIQ, PRI, WMI, PSI
Sorensen et al., 2011	Cross-sectional	144/ (5–7 years)	Acute and Chronic (LT)/BA, CD, MD, AHI, OT	WPPSI-III	↓ FSIQ, VQI, PRI, = PSI
Sorensen et al., 2014	Cross-sectional	93 (7–9 years)	Acute and chronic (LT)/ BA, CD, MD, AHI, OT	WISC-IV	↓ FSIQ, VQI = PRI, ↓WMI, PSI
Afshar et al., 2018	Cross-sectional	40 (6–16 years)	Chronic (LT) /BA, AD, A1AT, OT	WISC-IV	↓ FSIQ, VIQ, PRI, WMI, = PSI
Macedo et al., 2017	Cross-sectional	45/60 (2–7 years)	Chronic (LT)/ BA, CD, CR, A1AT, OT	TELD -3	↓ Receptive language = expressive language
Almaas et al., 2015	Cross-sectional	35/480 (4–12 years)	Chronic (LT) /BA, CD, A1AT, OT	M-ABC	↓General motor skills, manual dexterity, ball skills, balance
Ee et al., 2014	Cross-sectional	13/6 (6–17 years)	Chronic (LT) /BA, CD, A1AT, OT	WISC-IV	= FSIQ, VIQ, WMI, PSI
Haavisto et al., 2011	Cross-sectional	18/17 (7–16 years)	Acute and chronic (LT) /BA, AHI, OT	WISC-IIII	= FSIQ, VIQ
Caudle et al., 2012	Cross-sectional	33 (3–20 months)	Chronic (before LT) /BA	MSEL	↓ Receptive and expressive language, ball skills, = manual dexterity
Caudle et al., 2010	Cross-sectional	15 (4–21 months)	Chronic (before LT) /BA	MSEL	↓ Receptive and expressive language, ball skills, manual dexterity
Abu Faddan et al., 2014	Cross-sectional	35/23 (3–18 years)	Chronic (before LT) /HTC	Stanford–Binettest	↓ FSIQ
Gilmour et al., 2009	Logitudinal	20 (>47 months)	Chronic (LT) /BA, OT	WISC-IIII	↓ FSIQ, VIQ
Krull et al., 2003	Cross-sectional	15 (4–12 years)	Chronic (LT) /BA, A1AT, DC	WPPSI-R/WISC-III/CELF-P/CELFR	↓ FSIQ, VIQ, receptive, expressive and general language
Rodrigue et al., 2009	Cross-sectional	114 (9–11 years)	Chronic (pre – LT) /HTC	BRIEF T	↑WMI
Ng et al., 2018	Longitudinal	42 (<42 months)	Chronic (pre – LT) /BB	Bayley III	↓General language, gross motor skills
Wayman et al., 1997	Longitudinal (1year LT)	40 (<2 years)	Chronic (LT) /BB	Bayley	↓ FSIQ, general motor skills
Van Mourik et al., 2000	Longitudinal (1 year LT)	14 (<12months–5 years)	Acute and chronic (LT) /BA, A1AT, OT	GMAS	↓General language, ↑general motor skills, ball skills, ↓ manual dexterity
Stewart et al., 1989	Longitudinal (1 year LT)	14 (3 months–16 years)	Chronic (LT) /BA, A1AT, OT	WISC, MCDI	↓FSIQ, VIQ, general motor skills
Gold et al., 2017	Cross-sectional	13/5 (3–7 years)	Chronic (LT) /BA, A1A, OT	WPPSI-IV	= FSIQ
Stewart et al., 1991	Cross-sectional	28 (4–14 years)	Chronic (LT) /BA, A1AT, OT	WISC-R	= VIQ
Kaller et al., 2010	Cross-sectional	59 (6–18 years)	Chronic (LT) /BA	TAP	↓ WMI
Stewart et al., 1988**	Cross-sectional	21/15 (0–12 years)	Chronic (pre LT) BA, A1AT	WISC	↓ FSIQ, VIQ

*Average scores/no significant difference with norms / control groups. ↑ High scores/significantly higher than norms / control groups. ↓ Low scores/significantly lower than norms / control groups. LT: live transplantation; WPPSI/ WISC: Wechsler intelligence scales; FSIQ: full scale intelligence quotient; VIQ: verbal intelligence quotient; PRI: perceptual reasoning index; WMI: working memory index; PSI: processing speed index. BA: biliary atresia; CD: cholestatic diseases; MGD: metabolic genetic diseases; AT: acetaminophen toxicity; AD: autoimmune diseases; MD: Metabolic disorders; VI: viral infections; CR: cirrhosis; A1AT: alpha-1-antitrypsin deficiency; HTC: hepatitis C; ALF: acute liver failure; AHI: acute hepatic infections; IN: indeterminate; OT: others; CELFP / CELFR: clinical evaluation of language fundamentals; GMAS: griffiths mental ability scales; MCDI: Minnesota child development Inventory); TAP: test of attentional performance. **Results of children with early clinical manifestations under the age of 12 months.

NEUROPSYCHOMOTOR RESULTS AFTER LIVER TRANSPLANTATION

Full scale intelligence quotient – FSIQ

Fourteen studies evaluated the full total intelligence coefficient with WISC[5,9,12,14-19,26,28-31]. Eleven studies had no control group and the meta-analysis was made using the reference values of the instrument[5,9,12,15,17-19,28-30]. It was demonstrated that transplanted children aged 20 months to 18 years had a lower full IQ -0.41 (95%CI: -0.51 to -0.32; N: 9,973) compared to the group with reference values. The meta-analysis of the studies which had a control group[14,16,31] also showed a worse full IQ in transplanted recipients -0.53 (95%CI: -0.85 to -0.22; N: 165). All studies revealed a reduction in total IQ -0.42 (95%CI: -0.51 to -0.33; N: 10,138) (FIGURE 3.A).

Verbal intelligence quotient – VIQ

Thirteen studies investigated the VIQ with WISC[5,9,12,15-19,22,28-29,32]. The meta-analysis of studies compared with reference values showed that transplanted children and adolescents had worse verbal IQ -0.38 (95%CI: -0.57 to -0.18; N: 10,284). The same was seen in two studies conducted with control groups -0.47 (95%CI: -0.80 to -0.14: N: 147)[16,32]. The worst verbal IQ was maintained when the meta-analysis was made with all studies -0.39 (95%CI: -0.56 to -0.22: N: 10,431) (FIGURE 3.B).

Perceptual reasoning – PRI

Six studies investigated this variable with WISC[9,12,17-19,31]. Only one study had a control group, making it impossible to perform a meta-analysis between groups. The meta-analysis showed a decline in the Perceptual Reasoning Index in transplanted children aged 5 to 16 years, in relation to the reference values -0.30 (95%CI: -0.41 to -0.19; N: 5,483) (FIGURE 3.C).

Working memory – WMI

Seven studies evaluated working memory with WISC in the population aged 6 to 18 years[12,16-19,31,32]. The meta-analysis of the studies compared with reference values (5/7)[12,17-19,32] showed the worst performance in this variable -0.43 (95%CI: -0.56 to -0.30; N: 4,628). In the analysis of the studies which had a control group, it was observed that there was no statistically significant difference between groups -0.30 (95%CI: -0.63 to 0.03; N: 147)[16,31]. However, in the meta-analysis of the studies altogether, working memory was worse in transplanted patients -0.42 (95%CI: -0.54 to -0.29; N: 4,775) (FIGURE 3.D).

Processing speed – PSI

Seven studies evaluated this variable with WISC [9,12,16-19,31]. The meta-analysis showed worse cognitive processing speed -3.00 (95%CI: -4.67 to -1.33; N: 5,355) in the five studies compared with reference values [9,12,17-19] (20,11,21,14,22). Decline in this variable was also found in the meta-analysis of the studies which had a control group -7.20 (95% CI: -12.12 to -2.28; N: 147)[16,31], as well as in the general analysis -3.43 (95%CI: -5.02 to -1.85; N: 5,128) the PSI in the 5 to 18 year old sample (FIGURE 3.E).

Expressive and receptive language

Two studies evaluated expressive and receptive language in children aged 2 to 12 years. (FIGURE 3.F,G)[4,29]. The meta-analysis demonstrated that there was no statistically significant difference between groups in terms of expressive language -0.78 (95%CI: -1.99 to 0.42; N: 921). In turn, the meta-analysis showed lower performance in receptive language among transplanted children -0.85 (95%CI: -1.16 to -0.53; N: 921) in relation to the contrasted groups.

Motor skill

Four studies in this review evaluated general motor skills[15,23,26,27], although using different instruments. In 1989, Stewart et al.[15] evaluated motor skills before and after LT. They observed that there was an improvement in the scores after the surgical intervention (74.4±22.4; 75.4±21.4), although they still remained below expectations (values below 80 of the MCDI) in children with an average age of 4 years. In the 4 year prospective follow-up that Van Mourik et al. conducted in their population aged 12 months to 5 years, it was identified that this variable was not reduced in the pre-transplant sample (90.6±4.6); however, the scores only improved 1 and 4 years after LT (93.8±2.8; 97.3±4.4, respectively)[27].

Wayman et al.[26] also carried out a prospective study and evaluated children under 2 years of age in three moments: before, 3 and 12 months after LT. They found scores with a standard deviation (82.5±13) below the Bayley's normal values (100±15) in the moment pre-LT, which were reduced by two standard deviations (69±16.1) 3 months after the surgical procedure and were reestablished to pre-LT values 1 year later (80.9±8.7). Almas et al. found in a 4 year follow-up of a longitudinal cohort an impaired general motor function (8.12±1.88) compared to the control group (3.5±1.46). The M-ABC made it possible to assess other motor aspects that were affected, such as manual dexterity (3.5±1.74), when compared to the control group (1.24±0.9), and skill with the ball (1.75±1.18) and balance (1.62±1.3) when compared to healthy controls (0.6±0.6 and 0.47±0.6, respectively)[23].

NEUROPSYCHOMOTOR RESULTS OF CHILDREN AND ADOLESCENTS WITH NATIVE LIVER

Neurocognitive results (FSIQ, VIQ, WMI)

Stewart et al. in 1988[21] analyzed the verbal and total coefficients of children with clinical manifestations in the first year of life (2±3 months) and after that period (7±3.5 years) and identified that children with early symptoms had full and verbal IQ scores (85±8.8; 86.3±10.6 respectively) lower than those of children with late manifestations liver disease (99.5±13.8; 96.2±9.2) (FIGURE 4.A).

The meta-analysis demonstrated a lower FSIQ when compared to the control group -2.28 (95%CI: -4.26 to -0.29; N: 94) in two studies in children with preservation of their native livers aged between 2 months and 18 years[11,21].

Working memory (54±11) and other cognitive variables were not compromised in children with an average age of 11±3 years infected with hepatitis C virus in the initial stage of the disease in the study by Rodrigue et al., when compared with normal values (50±10)[33].

EXPRESSIVE AND RECEPTIVE LANGUAGE

Two studies checked the expressive and receptive language (FIGURE 4.B,C) using the MSEL instrument[10,24] in babies aged 3 to 21 months. The expressive language in the meta-analysis proved to be reduced compared to reference values -40.32 (95%CI: -79.74 to -0.89; N: 3,746) while receptive language scores. Receptive language did not show statistically significant differences between groups -31.85 (95%CI: -75.38 to 11.67; N: 3,746).

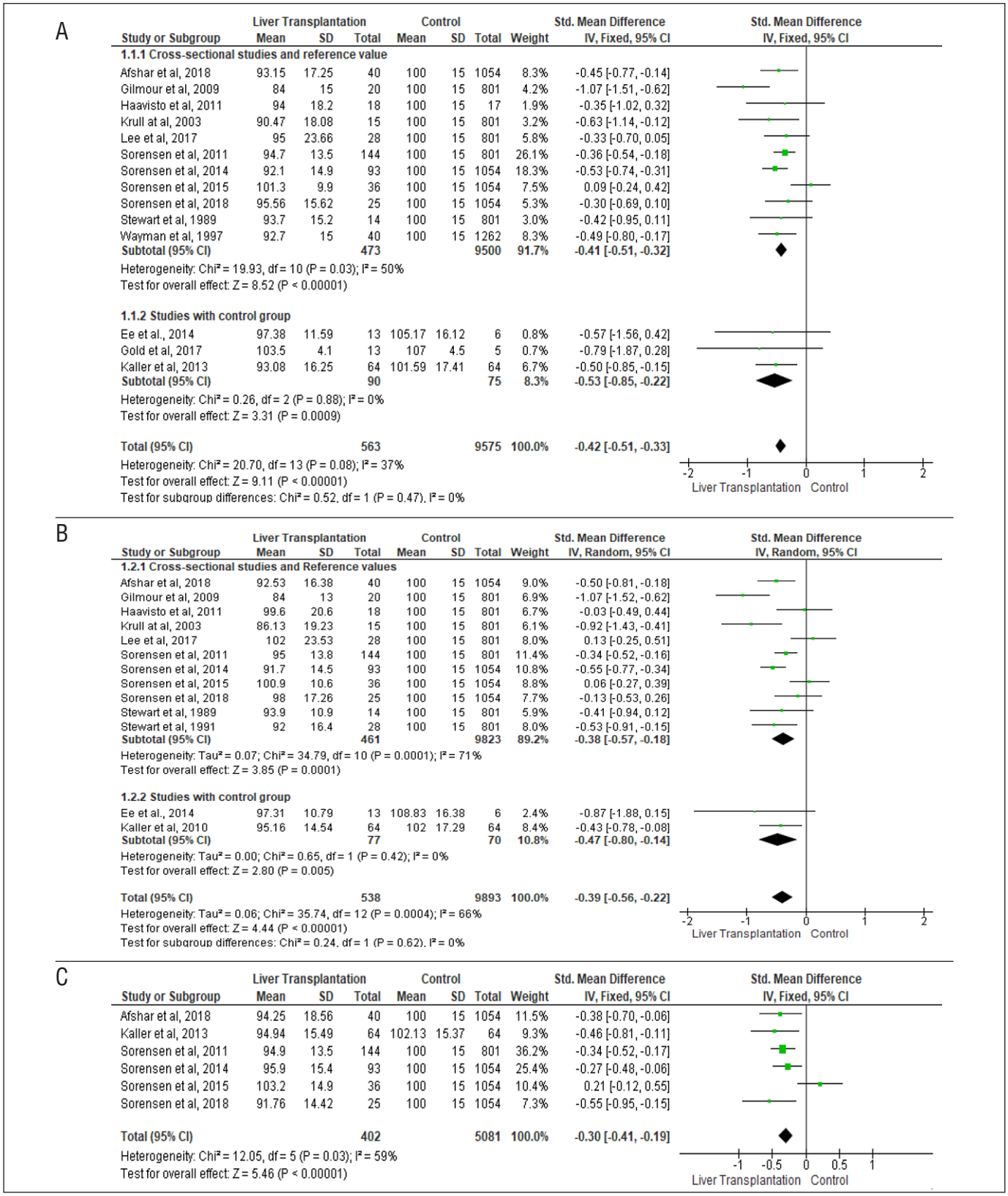

FIGURE 3. Meta-analysis comparing developmental aspects of children and adolescents after liver transplantation in the group control. **A.** FSIQ – full scale intelligence quotient. **B.** VIQ -verbal intelligence quotient. **C.** PRI – Perceptual Reasoning Index.

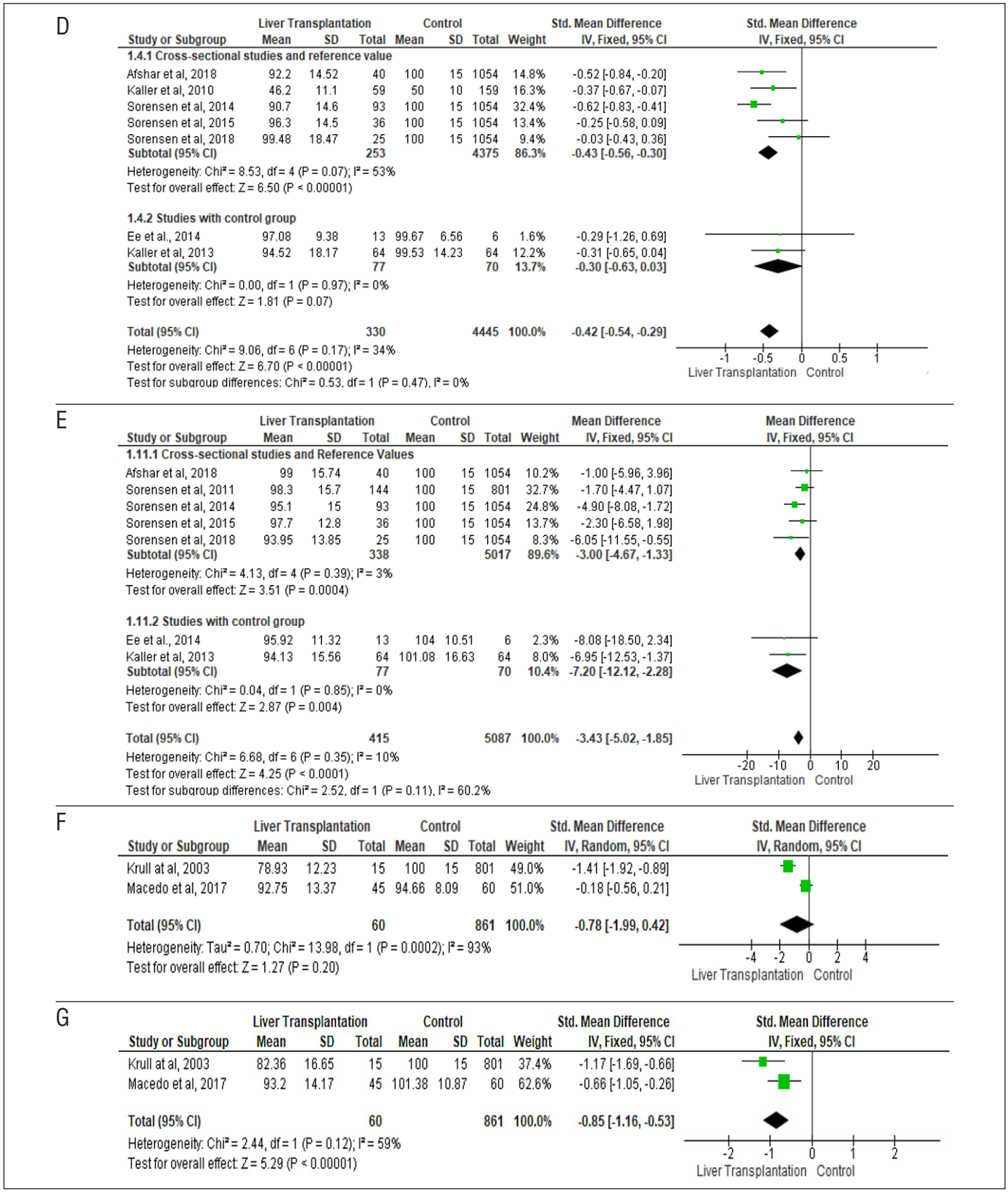

FIGURE 3. Meta-analysis comparing developmental aspects of children and adolescents after liver transplantation in the group control. **D.** WMI, Working Memory Index. **E.** PSI – Processing Speed Index. **F.** Expressive language and (G). **G.** Receptive language.

Manual dexterity

Two studies evaluated manual dexterity with MSEL[10,24]. The meta-analysis showed that there were no differences between the group with liver disease and the group with reference values -28.18 (95%CI: -72.20 to 15.84; N: 3,746) (FIGURE 4.D).

Ability with a ball

Two studies assessed ball skills with MSEL[10,24]. The meta-analysis showed that this ability was reduced in children with liver disease -46.29 (95%CI: -81.55 to -11.03; N: 3,746) compared to the groups with reference values (FIGURE 4.E).

NG et al. identified that 1-year-old children with BA presented a higher risk of delayed neurocognitive development even after hepatoportoenterostomy surgery. General motor (89.0±13.6) and language (92.5±14.4) skills presented low performance when compared with Bayley's normal values (100±15)[25].

DISCUSSION

In this systematic review, the meta-analysis indicates that children and adolescents with acute and/or chronic liver diseases have a deficit in neuropsychomotor development. With LT, these results improve, but many of them do not reach the neurodevelopment of healthy children. Those with their native livers also show low neurocognitive results. Children with hepatic manifestations in the first 2 years of life have lower neurodevelopmental scores because they are exposed to pathogenicity in the period of rapid development and maturation of the neural system, and because they remain with the liver disease longer.

Although LT improves patient survival, cognitive scores remain low and may compromise school performance and the future independence of these children and adolescents. Sorensen et al. reported in their multicenter study that children who received a

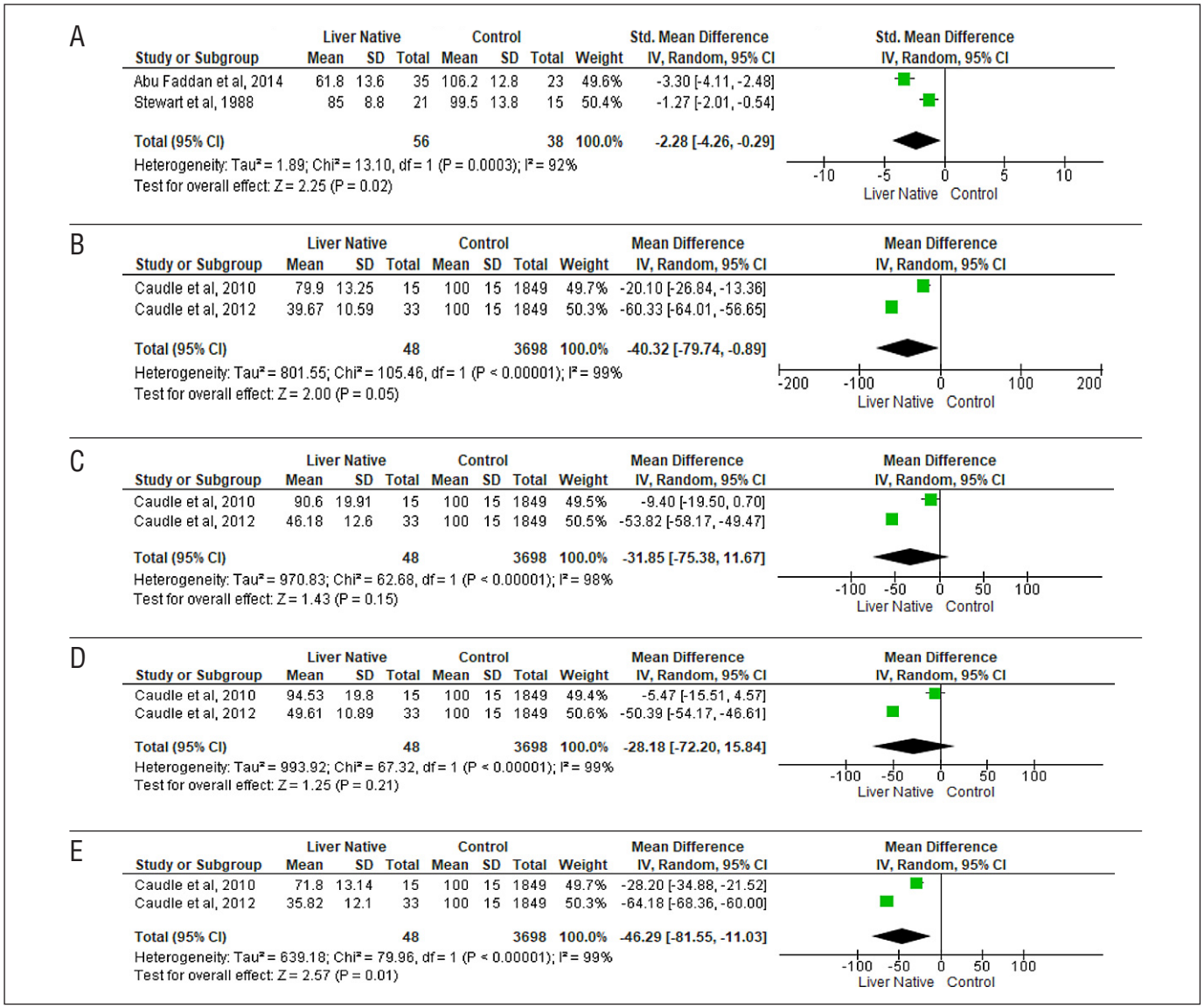

FIGURE 4. Meta-analysis comparing developmental aspects of children and adolescents liver native in the group control. **A.** FSIQ – full scale intelligence quotient. **B.** Expressive language. **C.** Receptive language. **D.** Fine motor. **E.** Gross motor.

liver transplant before the age of 5 years had twice the rate of intellectual delay and thrice the rate of learning difficulties compared to the general population[27,34]. The vulnerability of the nervous system in advanced liver disease in the first months of life worsens intellectual development, as this is the time of greatest neurological development. Associated with this, the waiting time to perform the transplantation procedure can enhance the deficits, especially in those children with chronic liver diseases when compared with those with acute liver diseases[28,31].

Neurotoxic aspects are important in the context of advanced liver disease and cirrhosis. Ammonia is the neurotoxin that best characterizes the pathogenesis of chronic encephalopathy in these patients. Residues of this substance accumulate in the systemic circulation, as the liver is unable to eliminate it. Such toxins cross the blood-brain barrier, and excess ammonia is able to cause changes in astrocytes and consequently generate hepatic encephalopathy[35].

In 2009, Gilmour et al.[28] identified an elevation of pre-LT serum ammonia and proved its correlation with low cognitive performance. The most relevant neurotoxicity in their study was due to elevation of calcineurin inhibitors, an immunosuppressant used after LT. They observed a worse performance in total and verbal IQ, since this medication can cause cumulative injuries and consequent neurological deterioration. (The authors Gilmour et al. justify their results of worse deficits when using this medication).

The general analysis of the studies showed that working memory was impaired in children and adolescents with liver diseases. Working memory is a system of limited capacity that allows temporary reservation and manipulation of information to perform complex skills such as language, learning and reasoning[36,37]. It is believed that the use of corticosteroids after LT can be toxic to the hippocampus, an essential area for learning and memory[34]. The study by Ee LC et al. evaluated children in a long-term approach post-LT (10 years post-LT), thus allowing a greater time for recovery in this score in relation to short-term studies[16]. They also used a sibling control group, preventing that the effect of genetic and family environment compromised the results. Kaller et al. argued that their cognitive scores were not significantly different from the average of the population without liver disease[17,32]. As the LT of their sample were performed in children younger than 12 months, that is, at an early moment, these children were less exposed to the disease, contradicting the literature, which shows that children affected in early childhood with liver diseases and submitted to LT have greater risk for cognitive delays[38]. Naturally, multiple factors contribute to full development and all cognitive and motor skills, the types of stimuli that these children receive, and the chronic diseases themselves can compromise this development.

Children performed worse in receptive language, the maturational course of language development occurs in an orderly manner, where the regions related to receptive language are myelinated earlier than those responsible for functions of expressive language[39]. This was perhaps a justification, because the study by de-Paula et al.[4], whose population had an average age of 17 months, influenced the result of the meta-analysis.

The meta-analysis of the group of children who remained with their native livers obtained opposite results to the group post-LT, that is, the expressive language was reduced, while receptive language showed no statistical differences. Nonspecific factors can influence language acquisition in children with liver disease, including social deprivation, malnutrition, family income and educational level of parents, in addition to methodological aspects of the studies included (reduced sample, different assessment instruments)[5,15,18,28]. It was clear that children with native livers had language deficit when compared to children post-LT, and even transplanted children did not achieve scores equal to those of healthy children without liver disease.

This review demonstrated that the motor capacity of children with liver disease was impaired. The time of exposure to the disease and its severity are crucial to the increase in neuromotor and cognitive deficits[6,18,21,25,29]. The underlying disease that compromises the multiple functions of the liver, malnutrition (which causes loss of muscle mass and weakness), the presence of ascites, and recurrent hospitalizations clearly diminish the opportunities for the performance of fundamental motor experiments in order to achieve a good development, impairing functional capacity at home and at school[40]. When submitted to transplantation, there was an improvement in survival and a reduction in mortality in these patients, but postoperative effects such as rejections, vascular problems, neurotoxicity of the drugs, reduced motor activity, together and in combination, can continue to impair fine and gross motor acquisition and development[15,40]. It is, therefore, suggested that surgical approaches to mitigate the effects of liver disease should be performed early, and children who cannot undergo immediate surgical treatment and also those who receive a conservative therapeutic approach require support from a multidisciplinary team to minimize the deleterious effects on neurodevelopment.

This study had as limitations the fact that the inserted articles presented heterogeneous liver diseases, time of follow-up in the cohorts (short- and long-term), assessment instruments, and age variation of children and adolescents.

In view of these outcomes and limitations, studies addressing specific liver diseases, particularly those more prevalent in the pediatric population, and with less variability in the age of the population and instruments for assessing neurodevelopment are recommended. Long-term follow-up can be a possibility to broaden the understanding of the academic and work performance of LT survivors. Children who remain with their native livers need to be better investigated at older ages, as there is a lack of studies with adolescents and young people. Knowing how these patients carry on their academic and professional lives after reaching adult age could confirm which therapeutic approaches are the best or which changes in medical care are necessary.

CONCLUSION

Acute or chronic liver disease can cause declines in cognitive, motor and language functions. Liver transplantation appears as a therapeutic possibility to reduce mortality and improve quality of life. Although the scores improve after LT, children with liver disease remain below average when compared to healthy children without chronic conditions. Early diagnosis and interventions in this population seem to be the path to less exposure to liver disease and less damage to neurodevelopment.

Authors' contribution

Santos JC, Saquetto MB, Gomes Neto M, Santos JL and Silva LR contributed substantially to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. They prepared and critically reviewed the manuscript, as well as approved the final version and are responsible for all aspects of the work.

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RESUMO – **Contexto** – A natureza da doença hepática, curso evolutivo e duração das hepatopatias, bem como grau de severidade e incapacidade podem desencadear desfechos múltiplos e com repercussões na aquisição e desenvolvimento neuromotores. **Objetivo** – Revisar sistematicamente e avaliar por meta-análise os efeitos da doença hepática sobre o desenvolvimento neuropsicomotor de crianças e adolescentes com seus fígados nativos e aquelas que realizaram transplante hepático. **Métodos** – As buscas foram realizadas nas bases de dados PubMed e periódicos Scopus desde as primeiras publicações na década de 1980 até junho de 2019, de estudos observacionais. Um valor de 0,05 foi considerado significativo. A heterogeneidade estatística do efeito do tratamento entre os estudos foi avaliada pelo teste Q de Cochran e o teste de inconsistência I2, no qual valores acima de 25 e 50% foram considerados indicativos de heterogeneidade moderada e alta, respectivamente. As análises foram realizadas com o Review Manager 5.3. **Resultados** – Vinte e cinco estudos preencheram os critérios de elegibilidade, incluindo 909 crianças e adolescentes com doenças hepáticas. As meta-análises mostraram déficits QI total -0,41 (IC 95%: -0,51 até -0,32; N: 9.973), QI verbal -0,38 (IC 95%; -0,57 até -0,18; N: 10.284) e linguagem receptiva -0,85 IC 95%: -1,16 até -0,53; N: 921) nos transplantes hepáticos e as com fígados nativos que apresentaram sintomas precocemente tinham escores de QI total e verbal (85±8,8; 86,3±10,6 respectivamente) menores do que aquelas com manifestações tardias (99,5±13,8; 96,2±9,2). Habilidade motora grossa apresentou-se reduzida -46,29 (IC 95%: -81,55 até -11,03; N: 3.746). **Conclusão** – A doença hepática aguda ou crônica pode determinar declínios nas funções cognitivas, motoras e de linguagem. Muito embora, os escores melhorem após transplante hepático, as crianças continuam abaixo da média quando comparadas às crianças sadias.

Palavras-chave – Doença hepática; transplante de fígado; desenvolvimento infantil.

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