(Supplementary file)

Paediatric brain MRI findings following congenital heart surgery: a systematic review

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2.1 Search strategy

Boolean operators included the following keywords and word combinations: ("congenital" OR "born with") AND ("cardiac" OR "heart") AND ("MRI" OR "magnetic resonance imaging" OR "MR") AND ("paediatric" OR "infant" OR "neonate" OR "newborn" OR "child*") AND ("surgery" OR "operation" OR "procedure" OR "surgical*") AND ("Brain" OR "cerebral" OR "neuro").

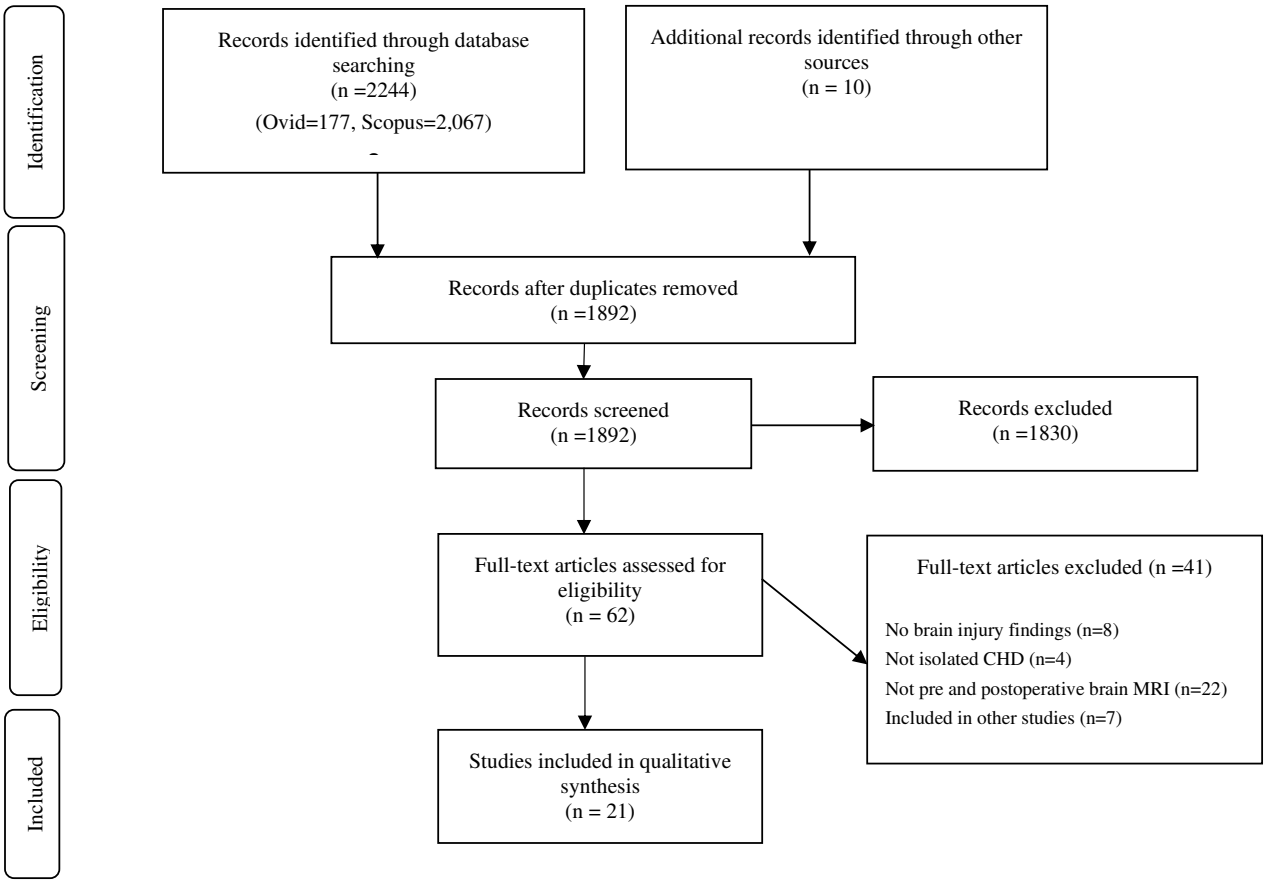


Figure 1: Flow diagram of study selection process (PRISMA).

Table 1: The P.I.C.O. search for systematic review question.

		Synonyms
P (Patients**)**	Paediatrics Congenital	Child, Infant, neonate, new-born, child Born with
I (Intervention**)**	Cardiac Surgery	Heart Operation, procedure, surgical
C (Comparison**)**	MRI pre- and post-surgery	Magnetic resonance imaging, MR
O (Outcome**)**	New brain MRI findings	Cerebral, neuro

2.3 Data extraction and quality assessment

The following data were extracted; The first author's name, journal, year of publication, Principal Investigator's location (Country), and study design (Cohort, Case-Control or Randomized Controlled Trial (RCT)) were extracted. Study population (sample size, sex, gestational age (weeks) and age at the time of surgery, Apgar score at 5 min, and CHD diagnoses were also recorded, with CHD diagnoses classified as single ventricle (1V) or two-ventricle (2V) conditions, transposition of the great arteries (TGA), aorta coarctation, or other lesions (including Ventricular outflow tract obstruction (VOTRO), Atrial septal defect (ASD), Ventricular septal defect (VSD), and Tetralogy of Fallot (TOF)). Where available, details of interventions were noted, including age of surgery and the use of cardiopulmonary bypass (CPB). The findings of any risk factor analyses were also noted. If neurodevelopmental outcome was assessed, the age of assessment, assessment tool, and score were recorded.

MRI details extracted included scanner manufacture (GE, Siemens, Philips) and field strength (1.5 T, 3 T), sequences used (T_1 or T_2 weighted, DWI, SWI, FLAIR, Proton Density (PD), Magnetic Resonance Spectroscopic Imaging (MRS), Magnetisation Prepared Rapid Gradient-Echo (MP-RAGE), and information provided (e.g., 3D volumetric information, detection of ischaemia or haemorrhage, diffusion tractography, or functional information). The method used to immobilise patients for their scans (sedation or no-sedation) and age at the time of the scans was also noted. Methods for reviewing and scoring MRI findings were summarised as either qualitative, or quantitative. If a scoring system was used, the details were noted. Data gathered from the scans included the number of patients with new and pre-existing findings, as well as information describing the number, type, and severity of lesions pre- and post- surgery, where this was available. Where linked data were available describing which patients with pre-operative findings went on to receive new bleeds or lesions, or enlargement of existing lesions, this information was preserved.

Variability in participant characteristics, interventions, and outcomes (clinical heterogeneity), and methodological diversity (methodological heterogeneity) were assessed through a narrative summary (table 2), and used to assess the suitability of existing studies for quantitative analysis.

Study	Sex	Gestational age	Apgar score at 5 min	Age at surgery	Age at pre-operative MRI	Age at post-operative MRI	Age at developmental assessment
McConnel (1990) **[1]**	×	×	×	×	×	×	×
Mahle (2002) **[2]**	✓	✓	×	✓	✓	✓	×
Partridge (2006) [3]	✓	✓	×	×	✓	✓	×
Dent (2006) **[4]**	✓	✓	✓	✓	✓	×	×
McQuillen (2007) **[5]**	×	×	×	×	✓	✓	×
Miller (2007) **[6]**	✓	✓	✓	×	✓	×	×
Block (2010) **[7]**	✓	✓	✓	×	✓	✓	×
Kwak (2010) **[8]**	✓	×	×	✓	×	×	×
Beca (2013) **[9]**	✓	✓	×	✓	×	×	✓
Drury (2013) **[10]**	✓	✓	✓	×	×	×	×
Mulkey (2013) **[11]**	✓	×	×	✓	✓	✓	×
Algra (2014) **[12]**	✓	✓	✓	✓	✓	×	✓
Andropoulos (2014) **[13]**	✓	✓	×	×	×	×	✓
Bertholdt (2014) **[14]**	✓	✓	✓	✓	✓	✓	✓
Lynch (2014) **[15]**	✓	✓	×	✓	×	×	×

Claessens (2018) **[16]**	✓	✓	×	✓	✓	×	✓
Peyvandi (2018) **[17]**	✓	✓	×	✓	✓	✓	×
Claessens (2019) [18]	✓	✓	×	×	✓	✓	×
Claessens (2019) **[19]**	✓	✓	×	✓	✓	✓	×
Lim (2019) **[20]**	×	✓	×	✓	✓	✓	✓
Guo (2019) **[21]**	✓	✓	✓	×	×	×	×

Table 2. Checklist for extracting information on patient characteristics, including age at the time of surgery, MR scans and developmental assessment.

2.4 Quality Assessment and data integrity

The Newcastle-Ottawa Scale includes three main categories: Selection, Comparability, and Outcome. High quality publications are allocated 'stars' for each numbered item within the 'Selection' and 'Outcome' categories, with a maximum of two stars awarded for 'Comparability'. Follow-up items under the 'outcome' category were always satisfied as post-operative brain MRI follow-up was essential for study inclusion. In the 'Comparability' category, confounding factors are controlled by their association with primary aim (pre- and post-MRI lesions prevalence and severity) and secondary aim (brain injury and developmental. This modified version of the Newcastle-Ottawa Scale (NOS) was used to assess the quality of both cohort and case-control studies.

Table. 3 Checklist of outcome information extracted to address the primary review aims.

Study	Secondary aim					
	Identification of MRI lesion	Subtype of MRI lesion	Number of patients acquired new lesions in patients with pre-existing lesions	Brain lesions risk factors		Developmental risk factors
McConnel (1990) **[1]**	✓	✓	×	×		×
Mahle (2002) **[2]**	✓	✓	✓	✓		×
Partridge (2006) [3]	✓	✓	✓	×		×
Dent (2006) **[4]**	✓	✓	×	✓		×
McQuillen (2007) **[5]**	✓	✓	✓	✓		×
Miller (2007) **[6]**	✓	✓	×	×		×
Block (2010) **[7]**	✓	✓	✓	✓		×
Kwak (2010) **[8]**	✓	✓	×	×		×
Beca (2013) **[9]**	✓	✓	✓		✓	✓
Drury (2013) **[10]**	✓	✓	×	×		×
Mulkey (2013) **[11]**	✓	×	✓	×		×
Algra (2014) **[12]**	✓	✓	×	✓		×

Andropoulos (2014) **[13]**	✓	✓	×	×	✓
Bertholdt (2014) **[14]**	✓	✓	×	✓	×
Lynch (2014) **[15]**	✓	✓	×	✓	×
Claessens (2018) **[16]**	✓	✓	✓	✓	×
Peyvandi (2018) **[17]**	✓	✓	×	×	×
Claessens (2019) **[18]**	✓	✓	×	×	×
Claessens (2019) **[19]**	✓	✓	×	✓	×
Lim (2019) **[20]**	✓	✓	×	✓	✓
Guo (2019) **[21]**	✓	✓	×	✓	×

Table 4. Modified New-castle Ottawa Scale for cohort studies

	Selection				Comparability*	Outcome	
First author, year	Representativeness of exposed cohort (Maximum: ⋆)	Selection of non-exposed cohort (Maximum: ⋆)	Ascertainment of exposure (Maximum: ⋆)	Demonstration that outcome of interest was not present at start of study (Maximum: ⋆)	Comparability of cohorts based on the design or analysis (Maximum: ⋆⋆)	Assessment of outcome (Maximum: ⋆)	Total score
McConnell, 1990	⋆	⋆	⋆	⋆	⋆⋆	⋆	7
Mahle, 2002	⋆	⋆	⋆	⋆	⋆⋆	⋆	7
Partridge, 2006	⋆	⋆	⋆	⋆	⋆⋆	-	6
McQuillen, 2006	⋆	⋆	⋆	⋆	⋆⋆	⋆	7
Dent, 2006	⋆	⋆	⋆	⋆	⋆⋆	⋆	7
Miller, 2007	⋆	⋆	⋆	⋆	⋆⋆	⋆	7
Block 2010	⋆	⋆	⋆	-	⋆⋆	⋆	6
Kwak 2010	⋆	⋆	⋆	⋆	⋆⋆	-	6
Bertholdt, 2014	⋆	⋆	⋆	⋆	⋆⋆	⋆	7
Andropoulos, 2013	⋆	⋆	⋆	⋆	⋆⋆	⋆	7
Beca, 2013	⋆	⋆	⋆	⋆	⋆⋆	⋆	7
Drury, 2013	⋆	⋆	⋆	⋆	⋆⋆	⋆	7
Mulkey, 2013	⋆	⋆	⋆	⋆	⋆⋆	-	6
Lynch, 2014	⋆	⋆	⋆	⋆	⋆⋆	-	6

Claessens, 2018	⋆	⋆	⋆	⋆	⋆⋆	⋆	7
Peyvandi, 2018	⋆	⋆	⋆	-	⋆⋆	-	5
Claessens, 2019	⋆	⋆	⋆	⋆	⋆⋆	⋆	7
Claessens NH, 2019	⋆	⋆	⋆	⋆	⋆⋆	⋆	7
Lim, 2019	⋆	⋆	⋆	⋆	⋆⋆	-	6
Guo, 2019	⋆	⋆	⋆	⋆	⋆⋆	⋆	7

Table 5. Quality assessment of included RCTs using Jadad scale.

Study quality	**Algra, 2014**
Described as randomized*	1
Described as double-blind*	1
Description of withdrawals*	0
Randomization method described and appropriate**	1
Double-blinding method described and appropriate**	0
Score	3

* A study receives a score of 1 for “yes” and 0 for “no”

** A study receives a score of 0 if no description is given, 1 if the method is described and appropriate, and -1 if the method is described but inappropriate.

3.1 Study and patient characteristics

Two groups were responsible for multiple publications; the Miller group in the US [6] [3] and Claessens group in the Netherlands [16] [18] [19]. Across all 21 records, 18 separate cohorts were studied (observational). Sample sizes ranged from 11 to 216 participants. Patients were recruited prospectively, except for two studies where data and images were examined retrospectively [13] [11]. Two studies included a healthy control group for observation and comparison [6] [14]. There was one RCT study randomised for either hypothermic circulatory arrest (DHCA) or antegrade cerebral perfusion (ACP) [12]. Studies were mostly single centre, although two studies involved two centres [7, 19] and one study involved three centres [21] (table 1).

3.3.2 Quantitative Brain Lesion Scores

The scoring system proposed by Block *et al.* (2010) scores each lesion as global, multifocal or focal. The severity of stroke, WMI, or intraventricular hemorrhage (IVH) was documented using a previously published brain lesion scoring system [7], [22], with single white matter (WM) lesions ≤3 mm in diameter classified as WMI; >3 mm lesions were classified as "stroke".

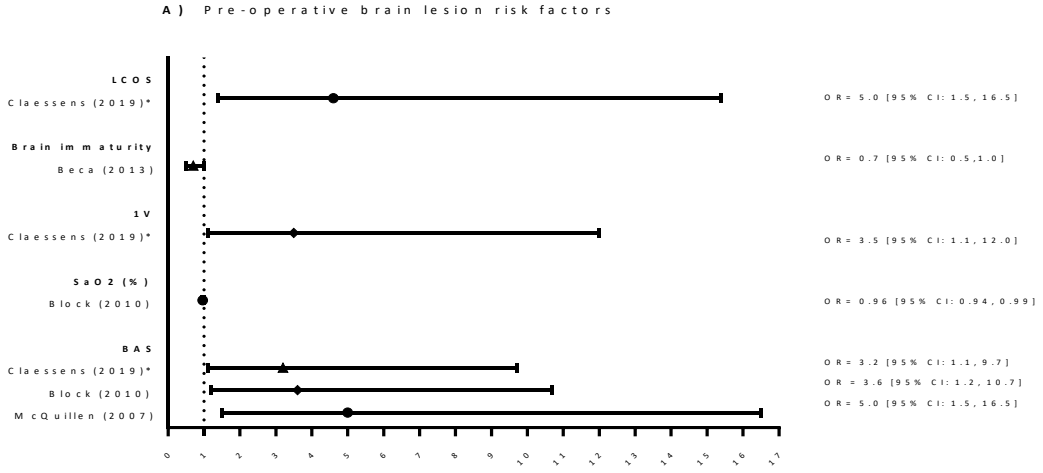
In a further study by Claessens *et al*. (2019): moderate-severe WMI was scored under two scenarios; first, if 3 or more WM lesions were found, each <2 mm in diameter; secondly, 2 or more WM lesions ≥2 mm in diameter. A stroke infarct was defined as a single WM lesion ≥2 mm [18]. Ischaemic lesions include multiple WMI lesions (mild (≤3 lesions, all ≤2 mm), moderate (4-6 lesions ≤2 mm or 2 lesions >2 mm), severe (>6 lesions or >2 lesions >2 mm or 5% involvement of the hemisphere), solitary WMI lesion >2 mm, and stroke. Hemorrhages were classified as intra-parenchymal (cerebellar hemorrhage, Grade 4 IVH) and extra-parenchymal (subdural hemorrhage, Grades 1-3 IVH). IVH graded into; Grade 1 (limited to germinal matrix or choroid plexus), Grade 2 (extension into normal sized ventricles), Grade 3 (extension into dilated ventricles), Grade 4 (combined with intraparenchymal hemorrhage) [19].

3.3.3 Neurodevelopmental Assessment

Neurodevelopmental risk factors are reported in a single study by Andropoulos 2014; new post-operative lesions were found to be a significant risk factor for lower Bayley scores at 12 months in both the cognitive and language domains [13]. Preoperative low rSO_2 (%) was identified as a risk factor for both cognitive and motor domains, and abnormal chromosomes for language and motor. Length of stay in the intensive care unit (ICU) was identified as a risk factor for all the three domains (cognitive, language, and motor) [13]. Other studies involving hypothesis or relationship tests explored risk factors such as age at the time of surgery, days of open chest [20] and brain immaturity [9].

4 Discussion

Significant risk factors (including estimates of effect size and confidence intervals) are summarised in figure 2. Balloon atrial septostomy (BAS) was predominantly reported as an influential pre-operative risk factor [19] [7] [5]. Low arterial oxygen saturation (SaO_2) [7] and LACOS [19] were significantly associated with both pre- and new post-operative MRI findings.



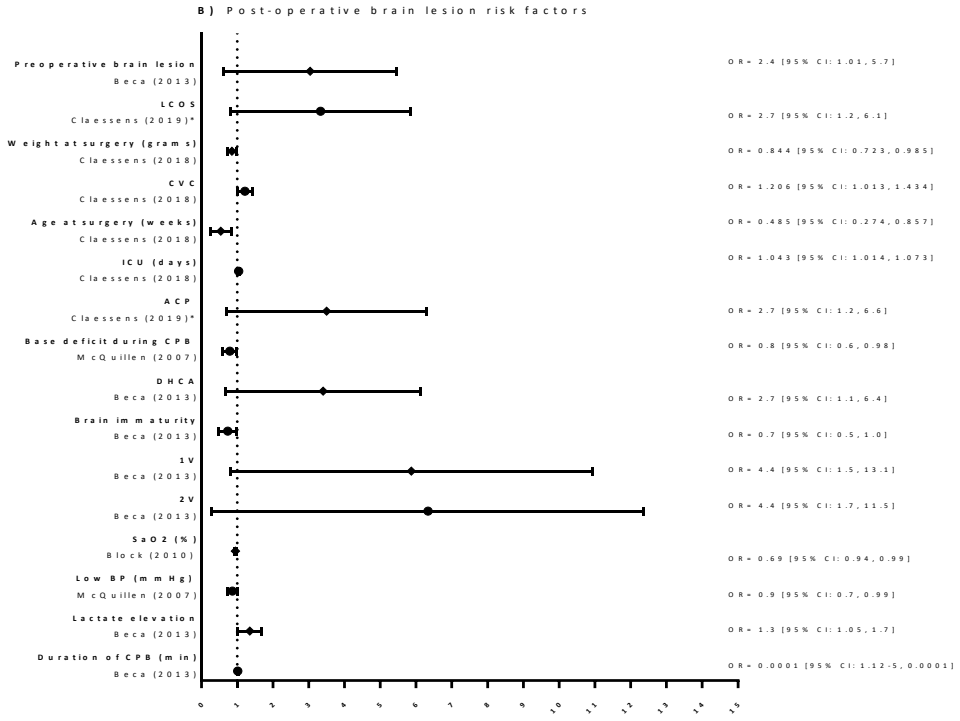


Figure 2. Summary of effect size and CIs for significant risk factors identified in the literature for A) Pre-operative brain lesions. B) Post-operative brain lesion. LCOS= low cardiac output syndrome, SaO_2= arterial oxygen saturation, CVC= central venous catheter, ACP= antegrade cerebral perfusion, DHCA= deep hypothermic circulate, ICU= intensive care unit, LOS= length of stay, rSO_2= regional cerebral oxygen saturation, BAS= Balloon atrial septostomy, 1V= one ventricle abnormality, 2V= ventricle abnormalities, CI= confidence interval, * [19].

References

[1] J. R. McConnell *et al.*, "Magnetic resonance imaging of the brain in infants and children before and after cardiac surgery: a prospective study," *American Journal of Diseases of Children,* vol. 144, no. 3, pp. 374-378, 1990.

[2] W. T. Mahle *et al.*, "An MRI study of neurological injury before and after congenital heart surgery," (in English), *Circulation,* Clinical Trial Research Support, Non-U.S. Gov't vol. 106, no. 12 Suppl 1, pp. I109-14, Sep 24 2002.

[3] S. C. Partridge *et al.*, "Pyramidal tract maturation after brain injury in newborns with heart disease," (in English), *Annals of Neurology,* vol. 59, no. 4, pp. 640-51, Apr 2006.

[4] C. L. Dent *et al.*, "Brain magnetic resonance imaging abnormalities after the Norwood procedure using regional cerebral perfusion," *The Journal of thoracic and cardiovascular surgery,* vol. 131, no. 1, pp. 190-197, 2006.

[5] P. S. McQuillen *et al.*, "Temporal and anatomic risk profile of brain injury with neonatal repair of congenital heart defects," *Stroke,* vol. 38, no. 2 PART 2, pp. 736-741, 2007.

[6] S. P. Miller *et al.*, "Abnormal brain development in newborns with congenital heart disease," *New England Journal of Medicine,* vol. 357, no. 19, pp. 1928-1938, 2007.

[7] A. J. Block *et al.*, "Clinically silent preoperative brain injuries do not worsen with surgery in neonates with congenital heart disease," (in English), *Journal of Thoracic & Cardiovascular Surgery,* vol. 140, no. 3, pp. 550-7, Sep 2010.

[8] J. G. Kwak, W. H. Kim, J. T. Kim, I. O. Kim, and J. H. Chae, "Changes of brain magnetic resonance imaging findings after congenital aortic arch anomaly repair using regional cerebral perfusion in neonates and young infants," (in English), *Ann Thorac Surg,* vol. 90, no. 6, pp. 1996-2000, Dec 2010.

[9] J. Beca *et al.*, "New white matter brain injury after infant heart surgery is associated with diagnostic group and the use of circulatory arrest," (in English), *Circulation,* Research Support, Non-U.S. Gov't vol. 127, no. 9, pp. 971-9, Mar 05 2013.

[10] P. P. Drury *et al.*, "Deep hypothermic circulatory arrest during the arterial switch operation is associated with reduction in cerebral oxygen extraction but no increase in white matter injury," (in English), *Journal of Thoracic & Cardiovascular Surgery,* vol. 146, no. 6, pp. 1327-33, Dec 2013.

[11] S. B. Mulkey *et al.*, "Multi-tiered analysis of brain injury in neonates with congenital heart disease," (in English), *Pediatric Cardiology,* vol. 34, no. 8, pp. 1772-84, 2013.

[12] S. O. Algra *et al.*, "Neurological injury after neonatal cardiac surgery: a randomized, controlled trial of 2 perfusion techniques," *Circulation,* vol. 129, no. 2, pp. 224-233, 2014.

[13] D. B. Andropoulos *et al.*, "The association between brain injury, perioperative anesthetic exposure, and 12-month neurodevelopmental outcomes after neonatal cardiac surgery: a retrospective cohort study," (in English), *Paediatric Anaesthesia,* vol. 24, no. 3, pp. 266-74, Mar 2014.

[14] S. Bertholdt *et al.*, "Cerebral lesions on magnetic resonance imaging correlate with preoperative neurological status in neonates undergoing cardiopulmonary bypass surgery," (in English), *European Journal of Cardio-Thoracic Surgery,* Research Support, Non-U.S. Gov't vol. 45, no. 4, pp. 625-32, Apr 2014.

[15] J. M. Lynch *et al.*, "Time to surgery and preoperative cerebral hemodynamics predict postoperative white matter injury in neonates with hypoplastic left heart syndrome," *The Journal of thoracic and cardiovascular surgery,* vol. 148, no. 5, pp. 2181-2188, 2014.

[16] N. H. P. Claessens *et al.*, "Clinical and neuroimaging characteristics of cerebral sinovenous thrombosis in neonates undergoing cardiac surgery," (in English), *Journal of Thoracic & Cardiovascular Surgery,* Video-Audio Media vol. 155, no. 3, pp. 1150-1158, 03 2018.

[17] S. Peyvandi *et al.*, "The association between cardiac physiology, acquired brain injury, and postnatal brain growth in critical congenital heart disease," (in English), *Journal of Thoracic & Cardiovascular Surgery,* vol. 155, no. 1, pp. 291-300.e3, 01 2018.

[18] N. H. P. Claessens *et al.*, "Brain microstructural development in neonates with critical congenital heart disease: An atlas-based diffusion tensor imaging study," *NeuroImage: Clinical,* Article vol. 21, 2019, Art no. 101672, doi: 10.1016/j.nicl.2019.101672.

[19] N. H. Claessens *et al.*, "Brain injury in infants with critical congenital heart disease: insights from two clinical cohorts with different practice approaches," *The Journal of Pediatrics,* vol. 215, pp. 75-82. e2, 2019.

[20] J. M. Lim *et al.*, "Associations between age at arterial switch operation, brain growth, and development in infants with transposition of the great arteries," *Circulation,* vol. 139, no. 24, pp. 2728-2738, 2019.

[21] T. Guo *et al.*, "White matter injury in term neonates with congenital heart diseases: Topology & comparison with preterm newborns," *Neuroimage,* vol. 185, pp. 742-749, 2019.

[22] T. O. Cheng, "That balloon atrial septostomy is associated with preoperative stroke in neonates with transposition of the great arteries is another powerful argument in favor of therapeutic closure of every patent foramen ovale," *The American journal of cardiology,* vol. 98, no. 2, p. 277, 2006.