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

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ABSTRACT

Objective This systematic review aimed to establish the relative incidence of new postoperative brain MRI findings following paediatric congenital cardiac surgery.

Design To distinguish perioperative changes from pre-existing MR findings, our systematic search strategy focused on identifying original research studies reporting both presurgery and postsurgery brain MRI scans. Patient demographics, study methods and brain MR findings were extracted.

Results Twenty-one eligible publications, including two case-control and one randomised controlled trial, were identified. Pre-existing brain MRI findings were noted in 43% (513/1205) of neonates prior to surgery, mainly white matter injuries (WMI). Surgery was performed at a median age of 8 days with comparison of preoperative and postoperative MR scans revealing additional new postoperative findings in 51% (550/1075) of patients, mainly WMI. Four studies adopted a brain injury scoring system, but the majority did not indicate the severity or time course of findings. In a subgroup analysis, approximately 32% of patients with pre-existing lesions went on to develop additional new lesions postsurgery. Pre-existing findings were not found to confer a higher risk of acquiring brain lesions postoperatively. No evidence was identified linking new MR findings with later neurodevelopmental delay.

Conclusion This systematic review suggests that surgery approximately doubles the number of patients with new brain lesions.

Key messages

What is already known on this topic?

- Paediatric cardiac surgery patients are at high risk of brain lesions but the clinical significance of these, and potential impacts on neurodevelopment are unclear.
- Comparison of presurgery and postsurgery MRI scans provides an important tool for distinguishing new from pre-existing MR findings.

What this study adds?

- Our results suggest that preoperative MR findings are present in approximately 43% of paediatric patients with congenital heart disease (CHD) prior to surgery.
- Approximately 51% of patients undergoing surgery experience new findings postoperatively.
- Pre-existing lesions were not found to be a significant risk factor for acquiring new postoperative findings.

INTRODUCTION

It has long been recognised that delivery, congenital heart disease (CHD) and open heart surgery all carry a risk to the brain, potentially negatively impacting neurodevelopmental outcomes.[1] The estimated prevalence of CHD is 9 per 1000 infants,[2] of which 3 per 1000 require surgical or catheter-based interventions early in life.[3] Due to advances in diagnostic imaging, surgical treatment and intensive care, more children with CHD now reach adulthood.[4] However, the impact of brain lesions on long-term developmental outcomes remains a cause for concern. Up to 50% of CHD infants go on to experience developmental or psycho-social issues, but whether these are linked to perioperative brain injury remains unclear.[5]

Paediatric brain MRI is gaining in popularity and is already being performed routinely at many centres, especially in the USA. Brain MR scans obtained before and after surgery have the potential to provide unique insights into the nature, severity and timing of brain lesions acquired around the time of surgery. Comparison of presurgery and postsurgery brain images provides a means of confidently separating surgery-induced changes from other sources of injury, especially where surgery is performed soon after delivery.[6]

MRI findings are commonly classified as focal ischaemic infarcts (including stroke), white matter injury (WMI) (including periventricular leukomalacia), cerebral sinovenous thrombosis (CSVT) and haemorrhage.[7] The nature, location and severity of brain MRI findings can be quantified using scoring systems that include both qualitative and quantitative image assessment.[8 9] The primary aim of this systematic review was to quantify the incidence of, and risk of acquiring, new MRI findings postsurgery. Secondary objectives included a preliminary exploration of factors associated with new MR findings, and whether surgery-related changes were associated with lower neurodevelopmental test scores. As the impact of surgery can only be determined by comparing presurgery and postsurgery MRI scans our inclusion criteria were limited to studies comparing presurgery and postsurgery MRI to identify new findings.

METHODS

A systematic search and data extraction was conducted and reported in accordance with the

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[10] to identify all studies reporting paired presurgery and postsurgery MRI scans in paediatric patients undergoing congenital cardiac surgery.

Search strategy

Our systematic review protocol was prospectively designed and registered with the PROSPERO database (Registration number: CRD42019158886). A comprehensive, systematic literature search was conducted in MEDLINE OVID and SCOPUS by two independent researchers (FA and HSAC). The search was limited to original peer-reviewed research conducted in humans and published in English between January 1990 and June 2021 (see supplemental file for search strategy).

Study eligibility criteria

After automated removal of duplicates, two researchers (FA and HSAC) independently screened study titles and abstracts for eligibility. Eligibility was assessed according to a PICO (patient-intervention-comparator-outcome) framework to extract all studies reporting preoperative and new postoperative brain MRI findings in paediatric patients (≤16 years) undergoing congenital heart surgery (online supplemental table 1). Articles identified as eligible by either reviewer were progressed to full text review with eligibility agreed by consensus. Reference lists and citations associated with eligible articles were searched by hand for additional relevant publications. All primary peer-reviewed original research studies, including randomised controlled trials, cohort, case-control studies and case reports, were eligible for inclusion. Conference abstracts were excluded.

Data extraction and quality assessment

Quality assessment and data charting were independently conducted by two reviewers (FA and HSAC) and agreed by consensus. Data were extracted from the full text of each article using a predefined checklist. Full details of data extraction, including parameters that were not reported, and an indication of heterogeneity, are provided in online supplemental tables 2 and 3. A total of seven studies were excluded due to their cohorts representing a subset of patients published elsewhere. We were careful to ensure that patients were not 'double-counted' due to multiple publications. For the case-control study, only the CHD group was included (ie, not healthy controls). For the randomised controlled trial (RCT), both groups involved patients with CHD, so were included.

A modified version of the Newcastle-Ottawa Scale (NOS) for observational studies, and a five-item scale developed by Jadad *et al*[11] for the RCT, were used to support quality assessment. Full details of our quality assessment and extraction methods are provided as an online supplemental file.

Due to the paired nature of the data, it was not appropriate to conduct a meta-analysis; findings are reported in a narrative format. Statistical analyses were performed using Prism GraphPad (V.7).

RESULTS

Our systematic search criteria returned a total of 2244 papers across two databases (online supplemental figure 1). Ten additional studies were identified by reviewing full text bibliographies. After removal of duplicate entries, and screening of abstracts and full text, 21 studies involving a total of 1277 patients were eligible for inclusion. Studies were methodologically diverse as well involving differences in patient's CHD conditions and surgical interventions. In terms of information directly addressing our primary review aims relating to MR findings, 6 out of 21 studies provided a full set of relevant information[12–17] (online supplemental table 3). Quality assessment scores suggested studies were of variable quality, ranging from a minimum of 3/7 to maximum of 7/7 for the NOS, and 3/5 based on the Jadad *et al* score. In six of the cohort studies, MR outcomes were not clearly reported. In two studies, it was unclear whether findings had been present preoperatively (online supplemental tables 4 and 5). For the RCT, the handling of withdrawals was not described. It was also unclear whether the person reviewing the MR images had been blinded to the intervention. However, as the aim of the RCT differed from that of our review, these issues would not have affected our findings.

Study and patient characteristics

Patient demographics, CHD condition, details of preoperative and postoperative MRI, and operative details are summarised in table 1. Data from a total of 1277 independent paediatric patients with CHD were identified for further analysis. Of these, the sex of the baby was specified for 1155 subjects, with 67% of babies reported as male. A summary of patient population characteristics shows that 35% of children were diagnosed with single ventricle abnormalities, 38% with transposition of the great arteries (TGA), 10% with two-ventricle abnormalities, 14% with other cardiac lesions and 3% with coarctation of the aorta. One study did not report the population CHD type.[9] Most studies included patients with multiple types of cardiac abnormality. The majority (76%) of included patients underwent surgery involving CPB with a median CPB time of 147 (range 47–200) min.

MRI protocol

MR scan sequences exhibited significant heterogeneity between studies, as can be seen in table 2. T1-weighted and T2-weighted imaging are used in up to 90% of studies, diffusion-weighted imaging and volumetric imaging in 60% of studies, while other sequences are performed non-routinely (5%–30% of studies). Non-sedated brain MRI was performed in approximately 23% (297/1277) of patients across six studies using the 'feed and sleep' technique, with most patients still receiving a sedative or anaesthetic drug during their scan.

Outcomes

Qualitative brain MRI findings

Of 1205 patients who received a preoperative brain MRI in the early days of life, 513 patients (43%) had at least one pre-existing brain MRI finding at the time of their first scan. The preop scan occurred at a median (IQR) of 5 (IQR: 4.6–6) days. Of these, 205 patients were reported with WMI (40%) and 153 patients with infarcts (30%). A further 58 haemorrhage (11%) and 63 CSVT (12%) neonates were reported. In one study, 'lesions' in 34 patients were reported but the severity and type were not specified[9] (see table 3).

A total of 1124 out of 1277 (88%) patients received a postoperative brain MRI conducted at a median (IQR) age of 13 (IQR: 7–19) days. This generated comparable paired presurgery and postsurgery MRI scans in 1075 patients, which were compared to identify new findings. Comparison of paired preop and postop MRI revealed 550 patients (49%) with new postoperative MRI findings: 301 WMI (55%), 161 infarct (29%), 50 haemorrhage (9%) and 28 with CSVT (5%). In 10 patients, the type of findings was unspecified.[9] Note that, for some subjects, more

Table 1 Summary of main patient and operative characteristics

Author (year) country	Study design	N (male: female)	CHD diagnosis 1V	2V	TGA	AC	OL	Gestational age at birth (weeks)	Age at surgery (days)	Age at preoperative MRI (days)	Age at postoperative MRI
McConnel (1990) USA[28]	Cohort (pro)	15 (NR)	1	NR	1	1	12	NR	NR	NR	NR
Mahle (2002) USA[12]	Cohort (pro)	24 (16:8)	13	11	NR	NR	NR	39.4 (36.0, 41.1)	4 (1, 24)	Day of surgery	8.5 (5–12) days after surgery Late scan: 4.5 (3–6) months
Partridge (2006) USA[13]	Cohort (pro)	25 (16:9)	3	NR	18	1	3	► No brain injury: 39.6 (37.7–41) days ► Preop injury: 39.3 (36.3–39.6) ► Postop injury:39.3 (38–41)	≤6	No brain injury:6 (2, 36) ► Preop injury: 4 (2, 13) ► Postop injury: 3.5 (1, 7)	► No brain injury: 16 (12–56) days ► Preop injury: 20 (16–36) ► Postop injury: 18.5 (14–43)
Dent (2006) USA[18]	Cohort (pro)	22 (15:7)	22	NR	NR	NR	NR	39 (36–41)	4 (1, 8)	Operation day 4 (1, 8)	9.5 (5–14) days
McQuillen (2007) USA[14]	Cohort (pro)	62 (NR)	18	12	32	NR	NR	NR	NR	► No brain injury: 5.5 ► With brain injury: 5	► No brain injury: 18.5 ► With brain injury: 19
Miller (2007) USA[19]	Case-control (pro)	41 (29:12)	12	NR	29	NR	NR	39.1 (38.2–40.0)	NR	5 (3–6)	NR
Block (2010) USA[15]	Cohort (pro)	92 (59:33)	62	NR	30	NR	NR	► At UBC: 39 (38–40) ► At UCSF: 39 (38–40)	► With preop injury: 9 (7–11) ► No preop injury: 7 (5–11)	5 (3–7)	21 (16–27)
Kwak (2010) Korea[29]	Cohort (pro)	11 (10:1)	NR	NR	NR	11	NR	NR	11 (5, 46).	NR	NR
Beca (2013) New Zealand[16]	Cohort (pro)	153 (98:55)	72	81	NR	NR	NR	38.8±1.6	7 (4–11)	NR	► Early MRI≈7 days after surgery ► Late MRI≈ 3 months of age
Drury (2013) New Zealand[30]	Cohort (pro)	18 (11:7)	NR	NR	NR	18	NR	► DHCA: 39 (37, 41) ► No DHCA: 40 (39–41)	NR	NR	NR
Mulkey (2013) USA[9]	Cohort (retro)	73 (46:27)	NR	NR	NR	NR	73	► No brain injury: 39 (38–39) ► With brain injury: 38 (37–39)	► No brain injury:7 (4–10) ► With brain injury: 8 (4–12)	No brain injury: 4 (2–10) With brain injury: 8 (4–13)	46±41
Algra (2014) The Netherlands[23]	RCT	37 (30:7)	12	5	2	1	17	► No new WMI: 39.5 (37.6–41.0) ► New WMI: 39.0 (35.3–41.0)	► No new WMI: 9 (8, 15) ► New WMI: 9 (5, 34)	8 (4, 34)	► No new WMI: 6 days[2 27] ► New WMI: 7 (2–12)
Andropoulos (2014) USA[20]	Cohort (retro)	59 (34:25)	27	12	20	NR	NR	38.4±1.2	NR	NR	NR
Bertholdt (2014) Switzerland[21]	Case-control (pro)	30 (22:8)	8	NR	22	NR	NR	39.3 (36.7–41.9)	NR	6 (1, 12)	13 (6–30)
Lynch (2014) USA[24]	Cohort (pro)	37 (18: 19)	37	NR	NR	NR	NR	38.9±0.8	4.2±1.9	NR	1 week after surgery
Claessens (2018) The Netherlands[17]	Cohort (pro)	40 (27:13)	16	NR	12	2	10	► CSVT negative:39.1 (38.8–40.1) ► CSVT positive:39.3 (37.6–40.4)	► CSVT negative:9 (8–15) ► CSVT positive: 9 (7–10)	► CSVT negative:7 (6–12) ► CSVT positive:6 (4–8)	CSVT negative: 6 (5–8) CSVT positive: 7 (6–9)
Peyvandi (2018) USA[31]	Cohort (pro)	79 (55:24)	30	NR	49	NR	NR	► d-TGA: 39.2 (38.8–39.6) * ► HLHS: 38.9 (38.4–39.3) *	► d-TGA: 8 (5.5–11) ► HLHS: 8 (6–11)	► d-TGA: 5 (3–6) ► HLHS: 5 (3–6)	► d-TGA: 17.5 (15–25) ► HLHS: 24[20–30]
Claessens (2019) The Netherlands[26]	Cohort (pro)	74 (49:25)	17	NR	26	NR	31	39.5 (38.7–40.6)	NR	5 (3–7)	8 (7–10)

Continued

Table 1 Continued

Author (year) country	Study design	N (male: female)	CHD diagnosis 1V	2V	TGA	AC	OL	Gestational age at birth (weeks)	Age at surgery (days)	Age at preoperative MRI (days)	Age at postoperative MRI
Claessens (2019) The Netherlands[22]	Cohort (pro)	124 (92:32)	33	14	77	NR	NR	▲ HSC: 39.1 (38.1–39.9) ▲ ▲ WKZ: 39.4 (38.7–40.4)	-≤60 days	▲ HSC: 4 (2–5) ▲ ▲ WKZ: 5 (3–7)	▲ HSC: 12[7–18] ▲ ▲ WKZ: 7 (7–10)
Lim (2019) Canada[27]	Cohort (pro)	45 (NR)	NR	NR	45	NR	NR	39 (35–41)	▲ Early repair: 7 (3, 13) ▲ ▲ Late repair 17 (14, 54	5 (1, 26)	21 (4–70)
Guo (2019) USA[25]	Cohort (pro)	216 (144:72)	64	NR	118	NR	34	▲ UBC: 39 (38–40) ▲ ▲ UCSF: 39 (38–40) ▲ ▲ UCZ: 39.2 (38.8–40.1)	≤3 months	40 weeks (38.6–41.2)	41.9 weeks (40.5–43.2)
Total		1277	447	135	481	34	180				

Age and time values presented as median (IQR) or median (min, max), median, mean±SD, mean (95% CI)* NR.
AC, aorta coarctation; ACP, antegrade cerebral perfusion; DHCA, deep hypothermic circulate; HSC, Hospital for Sick Children Toronto; NR, not reported; TGA, transposition of the great arteries; 1V, single ventricle abnormalities; 2V, two-ventricle abnormalities; WKZ, Wilhelmina Children's Hospital Utrecht.

than one category of MR finding was present. Although most studies reported the number of new WMI, or acute or chronic infarcts, fewer reported findings of haemorrhage[12 15 16 18–22] or CSVT[17 22 23] and the location and severity of new findings were rarely described in detail.

As most papers only reported totals and averages, the paired relationship between pre-existing and new findings was often unclear. Based on a more detailed analysis of 390 pairs of scans, from a subset of 7 papers providing sufficient information to deduce how many patients with pre-existing lesions went on to acquired new lesions; 32% (48/149) of paediatric patients with pre-existing lesions had additional new brain MRI findings following surgery.[9 12–17]

Risk factors related to presurgery and new postsurgery MRI brain findings were reported in 11 studies.[12 14–18 21–25]

Quantitative brain lesion scores

Four studies adopted an MRI brain lesion scoring system to quantify both the location and severity of findings.[9 15 22 26] Mulkey *et al*[9] developed a detailed brain MRI score to predict patients with CHD likely to be at greatest risk of neurodevelopmental delay. The scoring system ascribes a numerical value to each of 11 categories of brain lesion, and accounts for severity by considering the approximate number and size of areas affected. They concluded that brain lesion scores of 7/11 or higher would be concerning for neurodevelopmental delay. Full details of other scoring systems are provided as online supplemental file.

Neurodevelopmental assessment

A total of 232 infants across 7 studies underwent neurodevelopmental assessment between 1 and 2 years by either a paediatrician or psychologist. Most studies (five studies, n=207) used the third edition of the Bayley Scales of Infant and Toddler Development, when infants reached 2 years (three studies),[16 17 23] 18 months[27] or 12 months of age.[20] Based on these studies it is unclear whether there is any link between new postoperative MRI findings and low neurodevelopmental test scores. Neurodevelopmental risk factors are reported in a single study by Andropoulos *et al*[20] and full details are provided as an online supplemental file.

One study used a modified standardised assessment tool[21] to examine posture, general movements, tone, primitive reflexes and muscle stretch reflexes, cranial nerves and reactivity/behaviour in 22 neonates. Preoperative neuromotor assessment was performed at a median age of 7[2–13] days, providing a median sum score of 2 (range 0–6) out of a maximum score of 18. Postoperatively, 30 neonates with a median age of 15 (9–86) days had a median score of 2.5 (range 0–7). Children with preoperative brain MR lesions were found to have significantly poorer neuromotor preoperative score than neonates without brain lesions. There were no significant differences in postoperative neurodevelopment between neonates with and without either preoperative (p=0.55, Mann–Whitney U-test) or new postoperative brain lesions (p=0.96, Mann–Whitney U-test).[21] However, these findings need to be interpreted with caution, as one study, with only 22 patients is likely to be underpowered.

DISCUSSION

To the best of our knowledge, this is the first systematic review to focus on understanding the incidence of perioperative brain MRI findings associated with paediatric congenital cardiac surgery. Our findings suggest that CHD is consistently associated with a high proportion of patients experiencing both presurgery

Table 2 Summary of MRI protocols adopted by the included studies

MRI protocol	Outcome of interest	Studies
Scanner manufacturer	GE	McConnell,[28] Partridge,[13] Dent,[18] McQuillen,[14] Block,[15] Mulkey,[9] Bertholdt,[21] Peyvandi,[31] Guo[25]
	Philips	Mulkey,[9] Algra,[23] Andropoulos,[20] Claessens,[17] Claessens,[26] Claessens[22]
	Siemens	Mahle,[12] Block,[15] Beca,[16] Drury,[30] Lynch,[24] Lim,[27] Guo[25]
	Not reported	Miller,[19] Kwak[29]
Field strength	1.5 T	McConnell,[28] Mahle,[12] Partridge,[13] Dent,[18] McQuillen,[14] Block,[15] Beca,[16] Drury,[30] Mulkey,[9] Algra,[23] Andropoulos,[20] Lynch,[24] Claessens,[17] Peyvandi,[31] Claessens,[22] Lim,[27] Guo[25]
	3 T	Beca,[16] Bertholdt,[21] Claessens,[17] Peyvandi,[31] Claessens(19), Guo[25]
	Not reported	Miller,[19] Kwak[29]
Immobilisation	General anaesthetic	Mahle,[12] Dent,[18] Andropoulos,[20] Lynch[24]
	Sedation	Block,[15] Bertholdt,[21] Claessens,[17] Peyvandi,[31] Claessens[26]
	Feed and sleep	Block,[15] Bertholdt,[21] Claessens,[17] Peyvandi,[31] Claessens,[26] Lim[27]
	Not reported	McConnell,[28] Partridge,[13] McQuillen,[14] Miller,[19] Kwak,[29] Beca,[16] Drury,[30] Mulkey,[9] Algra,[23] Guo[25]
Image review	Single blinded observer (O), radiologist (R) or neuroradiologist (N)	McConnell,[28] Mahle,[12] Partridge,[13] Dent,[18] McQuillen,[14] Miller,[19] Block,[15] Kwak,[29] Drury,[30] Andropoulos,[20] Peyvandi,[31] Claessens[22]
	Pair of blinded observers (O), radiologist (R) or neuroradiologist (N)	Beca,[16] Mulkey,[9] Algra,[23] Bertholdt,[21] Lynch,[24] Claessens,[17] Claessens,[26] Guo[25]
	Not reported	Lim[27]
T1 weighted	Structural imaging (suppresses water and high signal intensity of fat)	McConnell,[28] Mahle,[12] Partridge,[13] Dent,[18] McQuillen,[14] Block,[15] Beca,[16] Drury,[30] Mulkey,[9] Algra,[23] Andropoulos,[20] Bertholdt,[21] Lynch,[24] Claessens,[17] Peyvandi,[31] Claessens,[26] Claessens,[22] Lim,[27] Guo[25]
T2 weighted	Detect pathology associated with oedema/fluid (high signal intensity of water)	McConnell,[28] Mahle,[12] Partridge,[13] Dent,[18] McQuillen,[14] Block,[15] Beca,[16] Drury,[30] Mulkey,[9] Algra,[23] Andropoulos,[20] Bertholdt,[21] Lynch,[24] Claessens,[17] Peyvandi,[31] Claessens,[26] Claessens,[22] Lim[27]
DWI and DTI	Acute cerebral infarct and haemorrhage (Brownian motion of water molecules)	Mahle,[12] Dent,[18], Beca,[16] Drury,[30] Mulkey,[9] Andropoulos,[20] Bertholdt,[21] Lynch,[24] Claessens,[17] Peyvandi,[31] Claessens,[26] Claessens,[22] Lim[27]
	Tractography (Brownian motion along direction of nerve fibres	McQuillen,[14] Miller,[19] Block[15]
FLAIR	High signal for lacunar Infarcts and subarachnoid haemorrhage.	Beca,[16] Drury,[30] Mulkey,[9] Algra[23]
SWI	Detects microhaemorrhages and calcium	Beca,[16] Mulkey,[9] Andropoulos,[20] Lynch,[24] Claessens,[17] Claessens,[26] Claessens[22]
3D/Volumetric	Detects abnormal brain region volumes	Partridge,[13] McQuillen,[14] Block,[15] Beca,[16] Drury,[30] Claessens,[17] Peyvandi,[31] Claessens,[26] Claessens,[22] Lim,[27] Guo,[25] Lynch[24]
MRS	Diagnoses metabolic brain disorders	Dent,[18] Miller[19]
Proton density	Evaluates grey/white matter abnormalities (grey matter has a higher signal intensity than the white matter)	McConnell[28]
MP-RAGE	Useful for brain tissue classification by offering excellent contrast for brain cortical segmentation	Lynch[24]
MR-venography	Examines the veins without the overlying tissues being visible (requires contrast material to enhance the visibility of the veins).	Claessens[22]

DWI, diffusion-weighted imaging.

and postsurgery brain MRI lesions. Based on comparison of pairs of images, just over half of neonates (51%) were reported with new brain MRI findings post-surgery, compared to 43% with pre-existing findings.

WMI was the dominant finding in both preoperative (40%) and new postoperative (55%) MRI scans. Focal infarcts were seen in 30% of patients preoperatively with additional new infarcts found in 29% of patients postoperatively. Haemorrhage and CSVT were investigated less frequently among studies. Haemorrhage was reported in 11% of patients preoperatively, with 9% of patients experiencing new lesions postoperatively. Some patients exhibited more than one type of finding and were represented in multiple categories.

Based on paired data, 32% (48/149) of patients with pre-existing lesions went on to acquire new lesions following surgery. This is lower than the 49% incidence overall and concurs with the results of a multivariable logistic regression analysis conducted by Block *et al* (n=92), suggesting that pre-existing lesions are not a significant risk factor for acquiring new postoperative findings.[15] Significant risk factors identified by previous studies are summarised in online supplemental figure 2.

It is important to note that these are radiological rather than clinically relevant diagnoses and some findings may simply reflect maturational or other differences. As many MRI findings represent minor lesions, which can resolve with time, or be mitigated through neuronal plasticity and adaptions of the growing brain, clinical significance is unclear.

It is worth noting that there have been significant improvements in MR imaging equipment and image quality over the last 30 years. Only one eligible paper was published in the 1990s, limited to 15 patients; this would not have contributed strongly to the review findings. Seven papers were published up to 2010 (inclusive) and 13 papers between 2011 and 2021. When we prospectively filed the review with PROSPERO, we were keen to capture all papers relevant to the topic regardless of publication date. In future reviews it may be beneficial to limit the search to recent publications to reduce heterogeneity.

Table 3 Number of patients with preoperative and postoperative brain MRI findings

Study	MRI scans			Preoperative MRI findings					New postoperative MRI findings					With preop findings
	Pre	Post	Paired	WMI	Infarct	Haemorrhage	CSVT	Total	WMI	Infarct	Haemorrhage	CSVT	Total	
McConnel *et al*[8]	15	15	15	NR	1	NR	NR	1	NR	1	NR	NR	1	NR
Mahle *et al*[12]	24	21	21	4	2	1	NR	7	9	4	7	NR	20	3/12
Partridge *et al*[13]	25	25	25	4	3	2	NR	7	5	1	NR	NR	6	2/7
Dent *et al*[18]	22	15	15	1	4	2	NR	7	7	8	1	NR	11	NR
McQuillen *et al*[14]	62	53	53	11	13	5	NR	29	14	5	NR	NR	19	7/29
Miller *et al*[19]	41	36	36	4	10	2	NR	14	9	3	0	NR	11	NR
Block *et al*[15]	92	78	78	21	23	7	NR	40	24	8	1	NR	32	13/33
Kwak *et al*[29]	11	11	11	NR	NR	NR	NR	NR	NR	1	NR	NR	1	NR
Beca *et al*[16]	153	135	135	30	7	6	NR	38	57	5	3	NR	59	7/27
Drury *et al*[30]	18	18	18	5	NR	NR	NR	5	5	NR	NR	NR	5	NR
Mulkey *et al*[9]	73	38	38	NR	NR	15	NR	34 (16 type is NS)	NR	NR	5	NR	28 (23 type is NS)	13/38
Algra *et al*[23]	37	36	36	18	3	5	3	29	22	9	2	38	71	NR
Andropoulos *et al*,[20] USA	59	59	59	12	9	4	NR	18	14	10	10	NR	28	NR
Bertholdt *et al*,[21] Switzerland	30	30	30	6	3	NR	NR	7	2	NR	NR	NR	2	NR
Lynch *et al*[24]	37	33	33	8	NR	NR	NR	8	16	NR	NR	NR	16	NR
Claessens *et al*[17]	40	40	40	NR	NR	NR	3	30	26	8	NR	11	45	3/3
Peyvandi *et al*[31]	79	73	73	16	18	NR	NR	34	22	8	NR	NR	30	NR
Claessens *et al*[26]	56	71	53	12	5	NR	NR	17	25	15	NR	NR	40	NR
Claessens *et al*[22]	100	120	100	16	48	8	57	100	37	74	21	12	124	NR
Lim *et al*[27]	45	45	45	14	4	1	NR	19	NR	1	NR	NR	1	NR
Guo *et al*[25]	186	172	161	23	NR	NR	NR	23	7	NR	NR	NR	7	NR
Total	1205	1124	1075	205	153	58	63	442	301	161	50	28	519	48/149

CSVT, cerebral sinovenous thrombosis; NR, not reported; WMI, white matter injury.

Heterogeneity among studies is clearly present. Although most studies reported totals for cohorts including more than one type of CHD condition, single ventricle abnormalities and TGA represented 73% of subjects. The altered neurovascular physiology in these conditions is likely to have a more significant impact on prenatal brain development than other forms of CHD, which are under-represented. Several eligible studies limited recruitment to patients with specific CHD conditions. Furthermore, our analysis did not distinguish between patients who had received cardiopulmonary bypass compared with non-bypass interventions.

Diagnostic accuracy levels are likely to differ between the selected papers due to the use of differing methods for lesion detection and classification. Few studies used a brain lesion scoring system, which makes accurate comparisons difficult without a consistent approach across studies. As MR findings may resolve with time,[12 21] variations in study design, sequences adopted, and the timing of postoperative brain MRI may also be responsible for differences in brain MR findings between studies.

Future work should be directed towards systematically examining different CHD subgroups, with robust ascertainment of brain lesions to enable improved risk stratification of patients with CHD. Development of a standardised MRI brain lesion scoring system for paediatric CHD would also be beneficial. Structured neurodevelopmental follow-up programmes may be useful to help improve developmental outcomes integrated with clinical care. However, we found no evidence to support a link between either preoperative or new postoperative MR findings around the time of surgery and neurodevelopmental delay. In conclusion, this systematic review confirms the presence of preoperative brain MR findings in approximately 43% of neonates, with 51% of babies found to have additional new MR findings postoperatively.

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(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").

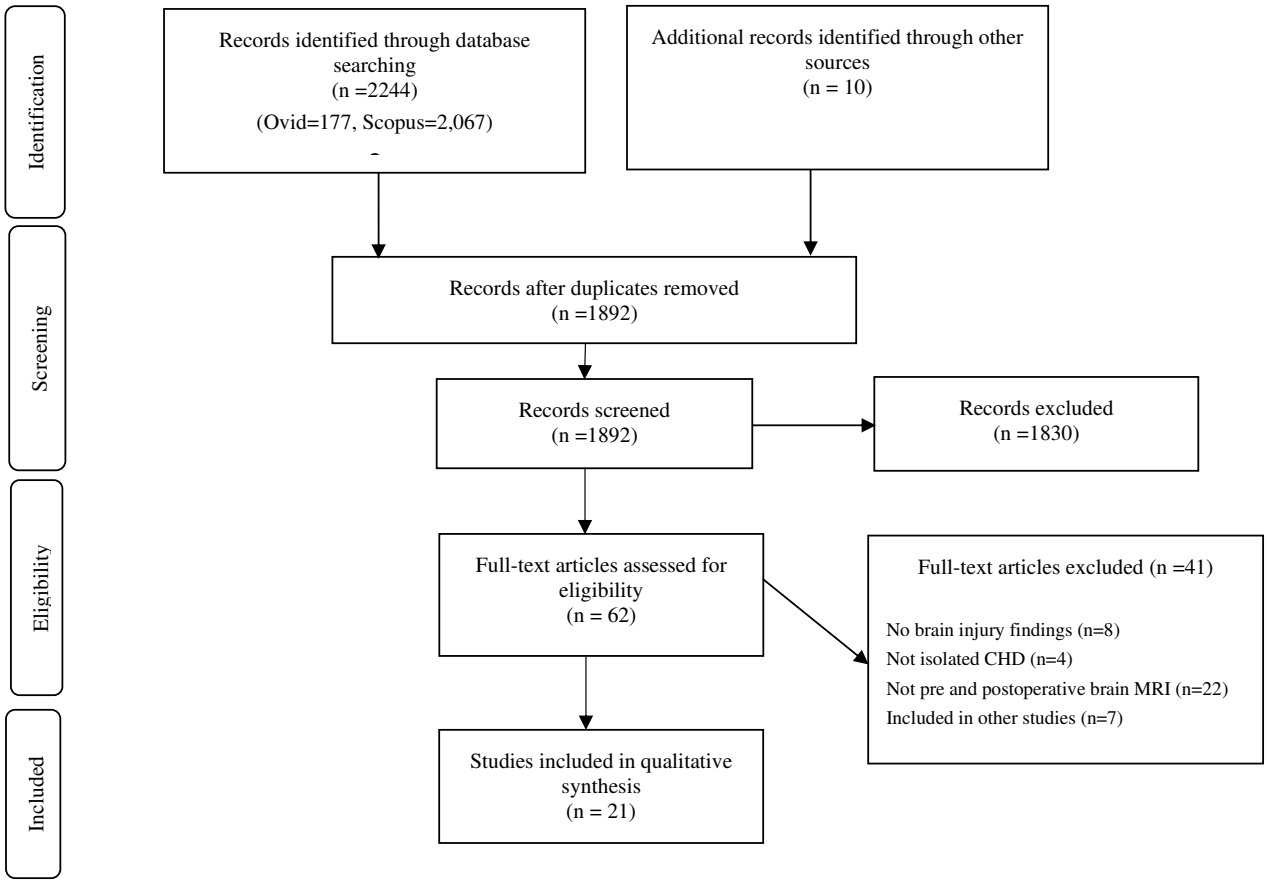


Figure 1: Flow diagram of study selection process (PRISMA).

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".

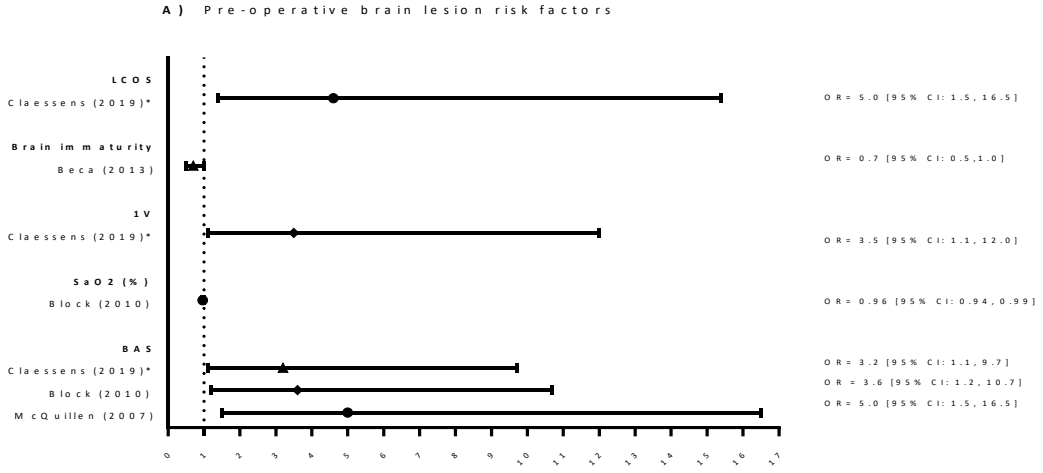
In a further study by Claessens *et al*. (2019): moderate-severe WMI was scored under two scenarios; first, if 3 or more WM lesions were found, each <2 mm in diameter; secondly, 2 or more WM lesions ≥2 mm in diameter. A stroke infarct was defined as a single WM lesion ≥2 mm [18]. Ischaemic lesions include 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.



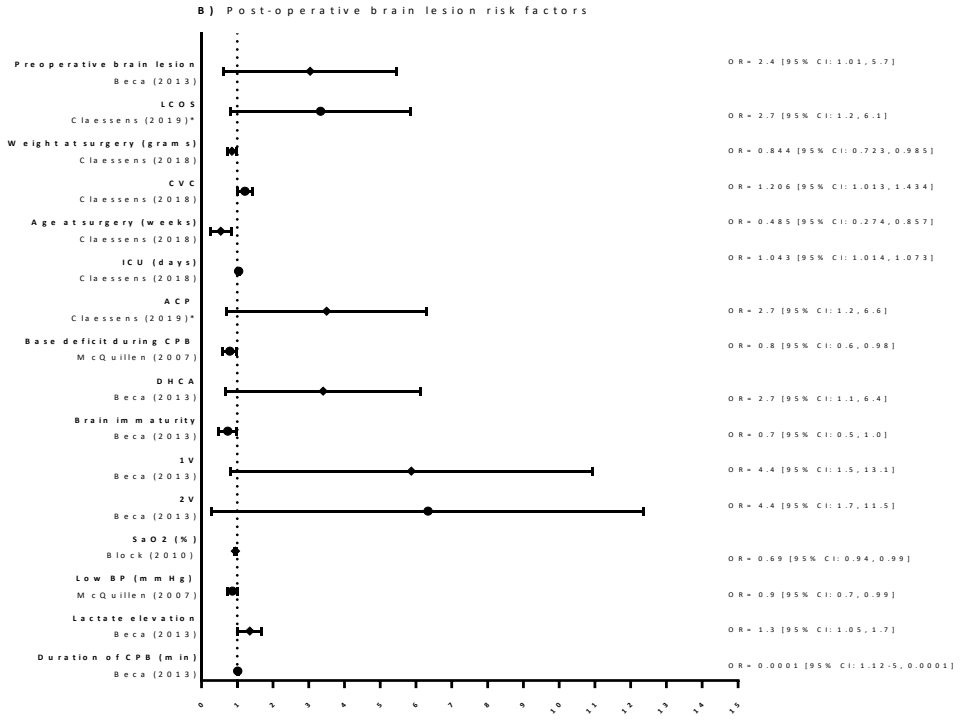


Figure 2. Summary of effect size and CIs for significant risk factors identified in the literature for A) Pre-operative brain lesions. B) Post-operative brain lesion. LCOS= low cardiac output syndrome, SaO_2= arterial oxygen saturation, CVC= central venous catheter, ACP= antegrade cerebral perfusion, 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].

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