Evaluation of neurodevelopmental impairments and risk factors in children following cardiac surgery: The first cohort from China

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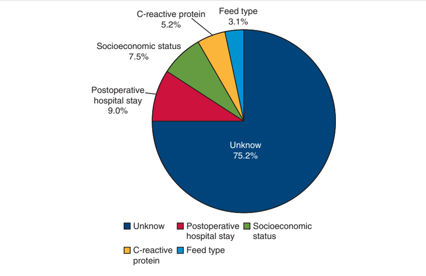
ABSTRACT

Objective: Neurodevelopmental impairment has been realized as the most common complication in children with congenital heart disease undergoing cardiac surgery during the past 30 years. But little attention has been paid to this problem in China. The potential risk factors for adverse outcomes include demographic, perioperative, and socioeconomic factors, which are vastly different in China compared with the developed countries in previous reports.

Methods: Four hundred twenty-six patients (aged 35.9 ± 18.6 months) at about 1- to 3-year follow-up after cardiac surgery were prospectively enrolled from March 2019 to February 2022. Griffiths Mental Development Scales-Chinese was used to evaluate the quotients of overall development and 5 subscales of the child's locomotor, language, personal-social, eye-hand coordination, and performance skills. Demographic, perioperative, socioeconomic, and feeding type during the first year of life (breastfeeding, mixed, or never breastfeeding) were examined to identify the risk factors for adverse neurodevelopmental outcomes.

Results: Mean scores were 90.0 ± 15.5 for development quotient, 92.3 ± 19.4 for locomotor, 89.6 ± 19.2 for personal-social, 85.5 ± 21.7 for language, 90.3 ± 17.2 for eye-hand coordination, and 92 ± 17.1 for performance subscales. For the entire cohort, the impairment in at least 1 subscale was found in 76.1% of the cohort (>1 SD below population mean) with 50.1% being severe (>2 SDs below the mean). The significant risk factors included prolonged hospital stay, peak level of postoperative C-reactive protein, socioeconomic status, and never breastfeeding or mixed feeding.

Conclusions: Neurodevelopmental impairment is substantial in terms of incidence and severity in children with congenital heart disease undergoing cardiac surgery in China. Risk factors contributing to the adverse outcomes included prolonged hospital stay, early postoperative inflammatory response, socioeconomic status, and never breastfeeding or mixed feeding. There is an urgent need for standardized follow-up and neurodevelopmental assessment in this special group of children in China. (JTCVS Open 2023;14:462-71)



Significant risk factors contributing to neurodevelopment requirement in our model.

CENTRAL MESSAGE

We found substantial neurodevelopmental impairment in incidence and severity in the first cohort of children with congenital heart disease at 1 to 3 years after cardiac surgery in China.

PERSPECTIVE

The significant risk factors contributing neurodevelopmental impairment included prolonged hospital stay, peak level of postoperative CRP, socioeconomic status, and never breastfeeding or mixed feeding. There is an urgent need for standardized follow-up and neurodevelopmental assessment in this special group of children in China.

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Abbreviations and Acronyms

CHD	= congenital heart disease
CPB	= cardiopulmonary bypass
CRP	= C-reactive protein
DHCA	= deep hypothermic circulatory arrest
DQ	= development quotient
ECMO	= extracorporeal membrane oxygenation
GDS-C	= Griffiths Mental Development Scales-Chinese
IQ	= intelligence quotient
NT-proBNP	= N-terminal-pro hormone BNP
SES	= Socioeconomic status
STS-EACTS	= Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery

As the survival for children undergoing cardiac surgeries of congenital heart defect (CHD) has improved, increased attention is being paid to their quality of life. An important component of quality of life is intellectual and neurological development. Thirty years ago, the influence of deep hypothermic circulatory arrest (DHCA) in children with transposition of the great arteries undergoing the arterial switch operation ushered in an era of intense research on brain injury and neurodevelopmental outcomes in simple or complex CHD undergoing cardiac surgery, which is now realized as the most common and potentially the most damaging complication.[1-11] These patients have been found to have problems with full-scale intelligence quotient (IQ), motor, language, and performance. Neurodevelopmental impairments have become so pervasive that in 2012 the American Heart Association and the American Academy of Pediatrics issued a joint scientific statement on guidelines for systematic surveillance, screening, evaluation, and management of developmental disabilities in an effort to optimize neurodevelopmental outcomes in this population.[8]

The etiology of neurodevelopmental impairment has emerged as complex and multifactorial, including innate patient (eg, lower birth weight and gestational age, genetic disorders, and single-ventricle physiology),[8,12-15] perioperative factors (eg, longer durations of DHCA and hospitalization)[2,7,9,11,16] as well as socioeconomic status (SES) (eg, maternal education).[8,11,14,16-18] The earliest prospective trials focused on intraoperative bypass management strategies as a potential modifiable risk factor for adverse neurodevelopmental outcome.[1,7] Subsequent data have shown the greater importance of sociodemographic and preoperative factors, and postoperative morbidity.[8,14] However, these factors together explain only one-third of the variance in neurodevelopmental outcomes, stressing the need for exploring new risk factors.[19] Furthermore, despite a rich literature, most of the research has been conducted in developed countries.

In China, due to historic reasons, there was delayed development of pediatric cardiology and surgery for about 20 years. Despite the fast improvement in surgical techniques and perioperative care, little attention has been paid to brain injury and neurodevelopmental outcomes.[20] More importantly, the risk factors that have been identified are vastly different in China compared with developed countries; for example, a broader range of age at operation, less complex CHD surgeries, and less advanced socioeconomic status. As such, the results that have been obtained may not be readily applicable to clinical practice in China.

We have implemented neurodevelopmental evaluation in our center for about 3 years. In this study, we set out to conduct a comprehensive analysis of neurodevelopmental outcomes and relevant risk factors in demographic characteristics, perioperative management, and SES in children with heterogeneous CHD at 1 to 3 years after cardiac surgery in the first cohort of 426 children in China.

PATIENTS AND METHODS

Patients

After the institutional ethics approval on December 2018 (No. 46201), informed consent was obtained at the Guangzhou Women and Children's Medical Center, 426 patients at about 1 to 3 years after cardiac surgery were prospectively enrolled from March 2019 to February 2022 when they came for follow-up and were available for the additional test on neurodevelopmental outcomes. Exclusion criteria included recognizable genetic syndromes, visual and hearing problems, any other medical complications limiting participation, or unplanned reinterventions and readmissions.

Neurodevelopmental Assessment

Griffiths Mental Development Scale-Chinese (GDS-C) was used, which is the only mental development scale that has been normed in China and covers most of our patients' ages.[21] GDS-C generates a development quotient (DQ) from the overall scale that represents a child's general intellectual ability. It also assesses 5 subscales of the child's locomotor, language, personal-social, eye-hand coordination, and performance skills. Each score is normed to have a mean of 100 ± 15. Thus, a score below 1 or 2 SDs of the population mean was considered as mild-moderate or severe developmental impairment. The neurodevelopment assessment was performed by a certified psychologist (J.F.)

Parenting and Socioeconomic Assessment

A self-report assessment was developed based on previous studies to indicate parenting and SES of each patient, including feeding mode (breastfeeding, mixed feeding, and never breastfeeding), parental age at child's birth, parental occupation, education level, and annual household income.[22] For each parent, education level was categorized as primary school or below, junior high school graduate or equivalent, high school graduate or equivalent, college graduate or equivalent; and bachelor's degree or above. Occupation included manual worker/farmer/unemployed; businessman or clerk; and professional, manager, or government employee. Final SES was presented as index of sum of annual household income and parental occupation and education scores (Appendix 1).

Intraoperative Procedures and Postoperative Managements

Standard cardiopulmonary bypass (CPB) procedures were performed in 391 (91.8%) patients as described elsewhere.[9]

Standard postoperative management was used as described elsewhere.[10] Despite the protocol, management varied among clinicians.

Demographic and Perioperative Data Collection

Demographic and clinical data are listed in Table 1 and Table E1. Clinical data included the Society of Thoracic Surgeons-European Association for Cardiothoracic Surgery (STS-EACTS) mortality category,[23] duration of pre- and postoperative mechanical ventilation, CPB, aortic crossclamp, DHCA, delayed sternal closure, cardiac intensive care unit, and hospital stay. Multiple times of CPB were recorded. Early adverse outcomes were defined as cardiac arrest and use of extracorporeal membrane oxygenation during hospitalization. Postoperative monitoring data included the peak values of central body temperature, serum lactate, daily serum C-reactive protein level (CRP) and N-terminal-pro hormone BNP (NT-proBNP) during the first 48 hours following cardiac surgery.

Statistical Analysis

Data were described as mean ± SD, median (interquartile range), or frequency (%) when appropriate. To screen for variables associated with neurodevelopmental assessment results, univariable linear regression was used to analyze their correlations with demographic, clinical, and SES variables. Multivariable linear regression analysis included the variables with $P < .10$ in the corresponding univariable analysis, and were presented as R^2 along with β confidents and percent contributions. Multivariable regression analysis was additionally performed based on the literature to select the risk factors. All analyses were performed with Stata Statistical Software version 17 (StataCorp) and SPSS version 16 (IBS-SPSS Inc).

RESULTS

Patients

Neurodevelopmental outcomes were assessed at 35.9 ± 18.6 months of age and are listed in Table 2. Median age at surgery was 4.6 months (interquartile range, 1.8-8.5 months). Median interval between assessment and surgery was 27.7 ± 15.8 months.

DHCA (19.9 ± 5.3 minutes) without antegrade selective cerebral perfusion was used in 31 (7.28%) patients for the repair of aortic arch obstructive abnormalities (coarctation of aorta with ventricular septal defect in 21 patients and interrupted aortic arch in 5 patients). CPB and aortic crossclamp were performed 2 times in 22 patients when a residual lesion was found after the initial CPB. Non-CPB surgery was performed in 35 (8.2%) patients to repair the coarctation of the aorta without ventricular septal defect and patent ductus arteriosus and pulmonary arterial banding.

Neurodevelopmental Outcomes

Mean scores were 90.0 ± 15.5 for DQ, 92.3 ± 19.4 for locomotor 89.6 ± 19.2 for personal-social, 85.5 ± 21.7 for language, 90.3 ± 17.2 for eye-hand coordination, and 92 ± 17.1 for performance subscales. For the entire cohort, the delay in at least 1 subscale was found in 76.1% of the cohort (>1 SD below population mean) with 50.7% having severe delay (>2 SDs below the mean).

TABLE 1. Demographic, parenting, and socioeconomic and perioperative details (n = 426)

Variable	Result
Demographic data	
Gender	
Male	244 (57)
Female	182 (43)
Delivery type	
Eutocia	272 (64)
Cesarean	154 (36)
Gestational age (wk)	38.4 ± 2.7
Birth weight (kg)	3.05 ± 0.57
Asphyxia history	26 (6.1)
Parenting and socioeconomic data	
Feeding method	
Breastfeeding	130 (30.5)
Mixed feeding	186 (43.7)
Nonbreastfeeding	110 (25.8)
Socioeconomic status	17 (12, 26.5)
Perioperative details	
Age at surgery (mo)	4.6 (1.8, 8.5)
Age at assessment (mo)	35.9 ± 18.6
Duration of surgery (min)	182 ± 86.4
Cardiopulmonary bypass times (min)	
None	35 (8.2)
Once	369 (86.6)
Twice	22 (5.2)
Cardiopulmonary bypass time (min)	107.6 ± 61.4
Aortic crossclamp time (min)	57.8 ± 30.7
Deep hypothermia circulatory arrest use	31 (7.3)
Deep hypothermia circulatory arrest time (min)	19.9 ± 5.3
Body temperature	37.9 ± 0.68
C-reactive protein	52.5 ± 36.5
Lactate	2.9 ± 2.1
NT-proBNP	12,252.9 ± 11,275.4
Duration of CICU stay (d)	5.6 ± 8.2
Duration pf hospital stay (d)	12.0 ± 10.1
Delayed pleural closure	12 (2.8)

Values are presented as n (%), mean ± SD, or median (interquartile range). *NT-proBNP*, N-terminal-pro hormone BNP; *CICU*, cardiac intensive care unit.

Correlations of Neurodevelopmental Outcomes with Demographic, Clinical, and Socioeconomic Variables

Uni- and multivariable regression analysis results are shown in Tables 3 and 4, respectively. On this basis, we established 6 significant multivariable regression models to explain GDS-C results over DQ and 5 subscales (*P* values < .001) (Table 4 and Figure 1). Among the variables examined, multivariate regression showed that the duration of hospital stay, SES, postoperative peak level of CRP, and mixed or never breastfeeding were significantly correlated with DQ and 5 subscales, with the duration of hospital stay being the most significant factor, which accounted

TABLE 2. Neurodevelopmental outcomes in 426 patients following cardiac surgery

Outcome	Mean ± SD	No. of patients		
		Normal (>85)	Mild-moderate impairment (70∼85)	Severe impairment (<70)
Quotient of development	90.0 ± 15.5	284 (66.7)	109 (25.6)	33 (7.7)
Locomotor	92.3 ± 19.4	304 (71.4)	73 (17.1)	49 (11.5)
Personal-social	89.6 ± 19.2	268 (62.9)	100 (23.5)	58 (13.6)
Language	85.5 ± 21.7	214 (50.2)	127 (29.8)	85 (20.0)
Hand-eye ordination	90.3 ± 17.2	285 (66.9)	105 (24.6)	36 (8.5)
Performance	92 ± 17.1	300 (70.4)	91 (21.4)	35 (8.2)

Values are presented as n (%) unless otherwise noted.

for 5.22% to 8.99% variability and dominated 31.4% to 60.4% of models (P values < .01). SES was the second most significantly and positively correlated with DQ and 5 subscales that accounted for 2.91% to 7.54% variability and dominated 17.5% to 39.6% of model (P values $\leq$ .07). This was followed by peak value of CRP and feeding types. Of note, feeding types, particularly breastfeeding or not, were not significantly correlated with SES or maternal education (P = .25 and .31, respectively).

DISCUSSION

For the cohort as a whole, the mean scores in DQ and the 5 subscales were in the low normal range. Put in other words, the deficits in at least 1 subscale were found in 76.1% of the cohort (>1 SD below population mean) with 50.7% being severe (>2 SDs below the mean). Risk factors included prolonged hospital stay, elevated postoperative CRP level, lower SES, and additionally mixed or never breastfeeding during the early months of life. These factors explained 25% of the variation in outcomes.

Previous studies have largely focused on homogeneous neonates with complex CHDs using DHCA; that is, children with complete transposition of the great arteries undergoing the arterial switch operation[1-6] and children with hypoplastic left heart syndrome and related anomalies undergoing the Norwood procedure.[8-10,24] Later studies have examined less complex and more diverse CHDs.[11,15,17] Overall, a majority of patients in our cohort had varied degrees of neurodevelopmental impairment. The figure was higher than previous reports (about 20% to 40%).[4,7,15,25] The scores of DQ and 5 subscales in our cohort appeared worse than those undergoing biventricular repair,[11,15,17] closer to those undergoing DHCA or with single-ventricle physiology undergoing palliative operations.[2,9,10,15] Of note, the stage 1 Norwood procedure for hypoplastic left heart syndrome and its similar anatomic variants is not presently performed in China, and these patients perform the worst at neurodevelopmental outcomes.

In our cohort, prolonged hospital stay was the most predominate factor influencing neurodevelopmental outcomes.[5,26] Newburger and colleagues[5] reported that among 160 patients with complete transposition of the great arteries undergoing the arterial switch operation, longer hospital stay after surgery was adversely associated at age 8 years neurodevelopmental outcomes, even when adjusted for perioperative and socioeconomic variables. In more detail, each day of extended hospital stay led to a reduction of 1.0 to 1.6 points in full-scale IQ and other domains (verbal, performance, math achievement).[5] A similar effect of prolonged hospital stay reported by Limperopoulos and colleagues.[25] They studied the neurodevelopmental outcomes of children undergoing a variety of palliative or corrective cardiac operations before age 2 years and returned for follow-up evaluation between ages 1 and 3 years. In this more diverse population, it was found that duration of hospital stay independently predicted adverse outcomes in scores on the Griffiths Medical Development Scales.[25] The latter group was similar to ours.

Prolonged hospital stay is a surrogate for the effect that pre-, intra- and postoperative characteristics and events interact on brain. We subsequently examined the determinants of hospital stay. In univariable analyses, duration of hospital stay was significantly and positively correlated with numerous perioperative factors, including preoperative mechanical ventilation, STS-EACTS mortality category, intraoperative variables (eg, operation time, CPB time, the use of DHCA), and postoperative variables (delayed sternal closure; duration of mechanical ventilation; and peak values of epinephrine, NT-proBNP, lactate, and CRP). In multivariable analysis, the significant determinants of longer hospital stay were operation time, postoperative mechanical ventilation time, delayed sternal closure, and peak value of lactate. The predominance of hospital stay and its related factors indicate suboptimal surgical techniques and perioperative management, which are potentially modifiable. Of note, STS-EACTS mortality category was a significant risk factor for prolonged hospital stay, but not for the ultimate neurodevelopmental outcomes in multivariable analysis. This is different from studies suggesting patient innate factors; that is, CHD types, are the main determinants for neurodevelopmental outcomes.[10,27] Whereas some studies suggested few clinically modifiable risk factors for adverse neurodevelopmental outcomes,[27] length of hospital stay and surgical skills have been

TABLE 3. Univariable regression analysis results of neurodevelopment outcomes with demographic, clinical, and socioeconomic variables

Variable	Developmental quotient		Locomotor		Personal-social		Language		Hand-eye ordination		Performance	
	R2.% (β)	*P* value	R2.% (β)	*P* value	R2.% (β)	*P* value	R2.% (β)	*P* value	R2.% (β)	*P* value	R2.% (β)	*P* value
Sex	0.6 (2.404)	.117	1 (−4.294)	.086	2.2 (5.77)	.002	1.3 (5.062)	.022	–		–	
Delivery type	1.7 (–4.064)	.01			1.5 (−4.657)	.016	1.3 (−4.848)	.031	1.2 (−3.747)	.033	1.3 (−3.881)	.024
Feed type	1.2 (−2.328)	.03	–		1.3 (−2.898)	.027	0.7 (−2.415)	.115	0.9 (−2.207)	.063	1.6 (−2.88)	.014
Birth weight	2.4 (0.004)	.003	1.6 (0.005)	.03	1.7 (0.004)	.012	–		0.3 (0.005)	.001	3.1 (0.005)	.001
Gestational age	1.6 (0.711)	.017	0.8 (0.686)	.128	–		1.3 (1.322)	.033	0.7 (0.551)	.104	1.7 (0.813)	.013
Age at surgery	1.4 (−0.039)	.015	1.7 (−0.06)	.02	–		–		3.4 (−0.066)	<.001	1.1 (−0.037)	.032
Age at assessment	1.8 (−0.026)	.006	3.6 (0-0.052)	.001	–		–		9.1 (−0.064)	<.001	–	
Socioeconomic status	8.2 (0.296)	<.001	4.1 (0.305)	.015	6.9 (0.321)	<.001	5.4 (0.326)	.002	3.4 (0.203)	.011	6.2 (0.26)	.001
STS-EACTS mortality category	2.2 (−2.171)	.002	3 (−3.464)	.002	0.9 (−1.679)	.055	–		1.6 (−1.997)	.01	1.4 (−1.865)	.015
Duration of surgery	1.6 (−0.023)	.009	3.1 (−0.43)	.002	–		–		2.5 (−0.032)	.001	1.7 (−0.026)	.008
Undergoing CPB	1.8 (−5.818)	.005	1.2 (−6.808)	.057	1.5 (−6.582)	.013	0.7 (−5.204)	.091	1.3 (−5.357)	.024	2 (−6.51)	.004
Duration of CPB	2.8 (−0.04)	.001	3.9 (−0.064)	<.001	0.6 (−0.022)	.132	–		4.3 (−0.055)	<.001	2.3 (−0.039)	.002
DHCA		–	–		–		–		–		–	
Delayed sternal closure	1.5 (−11.879)	.013	1 (−11.432)	.089	–		–		2.8 (−17.631)	.001	2.1 (−15.063)	.004
Mechanical ventilation time	3.9 (−0.045)	<.001	2.3 (−0.044)	.009	2.2 (−0.041)	.03	2.4 (−0.048)	.003	3.1 (−0.044)	<.001	6.2 (−0.063)	<.001
Postoperative peak temperature in 48 h		–	–		–		–		–		–	
Postoperative peak value of serum C-reactive protein	3.7 (−0.083)	<.001	3 (−0.103)	.002	1.3 (−0.06)	.021	0.7 (−0.05)	.1	4.7 (−0.103)	<.001	4.1 (−0.094)	<.001
Postoperative peak value of serum lactate	1 (−0.712)	.046	–		–		–		1.4 (−0.928)	.02	1.4 (0.938)	.018
Postoperative hospital days	8.8 (−0.453)	<.001	7.7 (−0.547)	<.001	3.8 (−0.358)	<.001	3.3 (−0.381)	<.001	7.5 (−0.463)	<.001	10.6 (−0.546)	<.001

STS-EACTS, Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery; *CPB*, cardiopulmonary bypass; *DHCA*, deep hypothermic circulatory arrest.

TABLE 4. Multivariate regression analysis results of neurodevelopment outcomes with demographic, clinical, and socioeconomic variables

Variable	Developmental quotient	Locomotor	Personal-social	Language	Hand-eye ordination	Performance
Postoperative hospital days						
R2.% (β)	8.99 (−0.484)	5.31 (−0.511)	7.57 (−0.528)	7.96 (−0.668)	5.22 (−0.38)	8.51 (−0.469)
Dominance.%	36.2	44.2	39.7	60.4	31.4	32.21
P value	<.001	.008	<.001	<.001	.006	<.001
Socioeconomic status						
R2.% (β)	7.54 (0.254)	3.92 (0.276)	6.56 (0.284)	5.22 (0.303)	2.91 (0.155)	6.03 (0.224)
Dominance.%	30.3	32.7	34.4	39.6	17.52	22.84
P value	<.001	.067	.001	.003	.049	.002
Postoperatibe peak value of serum C-reactive protein						
R2.% (β)	5.23 (−0.098)	–	2.29 (−0.72)	–	5.78 (−0.115)	7.96 (−0.129)
Dominance.%	21.1	–	12	–	34.79	30.13
P value	.003	–	.07	–	.002	<.001
Feed type						
R2.% (β)	3.1 (−4.097)	2.77 (−4.95)	2.64 (−4.332)	–	2.71 (−4.285)	3.91 (−4.885)
Dominance.%	12.4	23.1	13.9	–	16.28	14.82
P value	.008	.033	.025	–	.016	.002
Overall						
R2.% (β)	24.85 (99.7)	12.01 (97.4)	19.07 (97.83)	13.18 (88.22)	16.62 (103.25)	26.41 (103.96)
P value	<.001	.001	<.001	<.001	<.001	<.001

highlighted by others as significant risk factors for impairment.[5,28,29]

Another mechanism by which hospital stay and neurodevelopmental outcomes might be linked is through systemic inflammatory response. Our data also showed a significant albeit weak correlation of postoperative peak level of CPR and hospital stay. The peak CRP level was independently associated with adverse neurodevelopmental outcomes after adjusting for hospital stay, SES, and feeding type. This is consistent with our previous finding that in patients with functional single-ventricle physiology undergoing the Norwood procedure, CRP level, among the perioperative variables, was the only independent factor associated with adverse neurodevelopmental outcomes.[9]

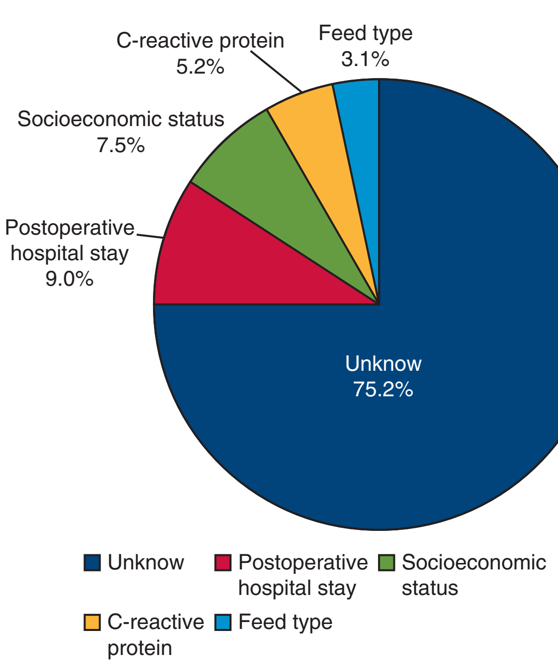

FIGURE 1. Variability of the significant risk factors (postoperative hospital stay, socioeconomic status, peak level of C-reactive protein, and feed type) contributing to neurodevelopment requirement in our model.

SES is known to have major influence on neurodevelopmental outcomes.[4,24] Wernovsky and colleagues[24] reported that in patients after the Fontan operation for a functional single ventricle, the percent variability in observed IQ explained by SES was 16%, whereas the percent variability explained by the use of circulatory arrest and other surgical variables was 6%. The influence of SES is multifactorial, beginning prenatally, and closely intertwined with factors such as maternal education. Studies have demonstrated the significant association of maternal education with neurodevelopment in children with CHD.[14,30]

Another significant risk factor for adverse neurodevelopment identified in our cohort was never breastfeeding or mixed feeding during the first year of life compared with breastfeeding. Although not reported in children with CHD, our finding is hardly surprising. There is a solid evidence base showing that breast milk feeding in healthy, full-term infants improves cognitive abilities in childhood, adolescence, and adulthood.[31,32] A meta-analysis of 17 observational studies reported that breast milk feeding was associated with higher scores in intelligence tests.[31] In premature children, never breastfeeding is a risk factor of suboptimal cognition at 2 years of corrected age.[33] Children with CHD are particularly vulnerable to poor nutrition and failure to thrive before cardiac operation as a result of disturbed hemodynamics.[34] Poor nutrition is common in infants with CHD.[35] This problem is further compounded by the complex metabolic alterations with hypermetabolism and hypercatabolism during the early postoperative course and is persistent through the first 6 months after operation.[36] Adequate nutrition with breast milk feeding in these children may be even more significant to improve their neurodevelopment outcomes.

Limitations

This study has several limitations. We performed neurodevelopmental assessment in only about 15% of patients undergoing cardiac surgery. There might be potential bias in our results. Our study was conducted in 1 relatively advanced tertiary care center, thus limiting the generalizability of our results in China. The factors contributing neurodevelopment impairment may vary among centers and regions. Routine chromosomal analysis was not performed. It is therefore possible that some patients; for example, those with 22q11 deletions who did not overtly manifest the velocardiofacial syndrome, were included in the study. We used the GDS-C instead of Beylay or Wechsler Intelligence Scales that were used in most of previous studies. GDS-C is the only scale that is normed in China,[21] but might introduce some bias. We examined patients only 1 to 3 years after cardiac surgery. Long-term follow-up is warranted.

CONCLUSIONS

Neurodevelopmental impairment is substantial in terms of incidence and severity in children with CHD undergoing cardiac surgery. Risk factors contributing to the adverse outcomes include prolonged hospital stay, early postoperative inflammatory response, and SES, and mixed or never breastfeeding. The perioperative management factors (eg, duration of pre- and postoperative time of mechanical ventilation; operation time; and peak values of epinephrine, NT-proBNP, lactate, and CRP) contributing to prolonged hospital stay are potential modifiable. Efforts should be made to improve the quality of management to improve neurodevelopmental outcomes. There is an urgent need for standardized follow-up, neurodevelopmental assessment, and interventions in this special group of children in China.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they have a conflict of interest. The editors and reviewers have no conflicts of interest.

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Key Words: congenital heart disease, cardiac surgery, neurodevelopment, China

APPENDIX 1. PARENTING AND SOCIOECONOMIC ASSESSMENT

Thank you for participating in this survey. These questions will take you a few minutes. Please answer the following questions truthfully. If you have any questions, please contact our researchers in time.

1 Child's name
2 Hospital ID
3 Birthday
4 Relationship
   A. Father
   B. Mother
   C. Other
5 Feed type
   A. Breastfeeding
   B. Mixed
   C. Never breastfeeding
6. How many months did you breastfeed?
7. Has the child attended kindergarten/nursery?
8. On average, your child spends ___hours watching an electronic screen every day.
9. Father's age at child's birth.
10. Mother's age at child's birth.
11. Father's education level
   A. Primary school or below
   B. Junior high school
   C. High school/vocational school
   D. Junior college/vocational college
   E. Bachelor's degree or above
12. Mother's education level
   A. Primary school or below
   B. Junior high school
   C. High school/vocational school
   D. Junior college/vocational college
   E. Bachelor's degree or above
13. Father's occupation type
   A. Manual worker, farmer, or unemployed
   B. Businessman or company employee
   C. Professional, manager, or civil servant
14. Mother's occupation type
   A. Manual worker, farmer, or unemployed
   B. Businessman or company employee.
   C. Professional, manager, or civil servant
15. Annual household income:___RMB

TABLE E1. Society of Thoracic Surgeons- European Association for Cardio-Thoracic Surgery mortality category in 426 patients following cardiac surgery

Category	n (%)
I	143 (34)
VSD repair	114
ASD repair	18
PAPVC repair	5
AVC (AVSD) repair	3
Vascular ring repair	2
DCRV repair	1
II	125 (29)
TOF repair	48
PDA closure	25
Coarctation repair	14
RVOT procedure	13
Valvuloplasty	9
Cor triatriatum repair	4
Pulmonary artery origin from ascending aorta repair	3
Aortopulmonary window repair	2
Aortic stenosis, repair	2
PAPVC, scimitar, repair	2
Anomalous origin of coronary artery repair	2
Pacemaker implantation, permanent	1
III	66 (15)
Coarctation and VSD repair	22
AVC (AVSD) repair, complete AVSD	18
Conduit placement, RV to PA	9
Pulmonary artery sling repair	9
Arterial switch operation	7
REV	1
IV	92 (22)
TAPVC repair	23
Fontan revision	19
ASO and VSD or aortic arch repair	17
DORV, intraventricular tunnel repair	14
Interrupted aortic arch repair	5
Unifocalization MAPCA(s)	5
Congenitally corrected TGA repair	4
Atrial septal fenestration	3
Ebstein's repair	1
Ross-Konno procedure	1

VSD, Ventricular septal defect; *ASD*, atrial septal defect; *PAPVC*, partial anomalous pulmonary venous connection; *AVC*, atrioventricular canal; *AVSD*, atrioventricular septal defect; *DCRV*, double chambered right ventricle; *TOF*, tetralogy of Fallot; *PDA*, patent ductus arteriosus; *RVOT*, right ventricular outflow tract; *RV*, right ventricle; *PA*, pulmonary artery; *REV*, REV procedure; *TAPVC*, total anomalous pulmonary venous connection; *ASO*, arterial switch operation; *DORV*, double outlet right ventricle; *MAPCA*, major aortopulmonary collateral arteries; *TGA*, transposition of the great arteries.