Developmental and emotional behavioural outcomes after COVID-19 febrile seizures: A single-centre experience

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ABSTRACT

Introduction: Children with febrile seizures often experience favourable long-term outcomes. However, the outcomes of COVID-19 febrile seizures remain uncertain. The study investigated the developmental and emotional/behavioural outcomes of children with and without COVID-19, presenting with febrile seizures.

Materials and Methods: Participants were families of children with febrile seizures admitted from January to April 2022, during the peak of COVID-19 Omicron variant infection cases. The children were assessed 9-18 months after the seizure event, using the Schedule of Growing Skills II developmental screening tool and their parents completed the Strengths and Difficulties Questionnaire, a measure of emotional/behavioural outcome. A child with positive COVID-19 is characterised by the presence of respiratory symptoms and a positive COVID-19 rapid antigen test. We compared the outcomes of children with and without COVID-19 using Fisher's exact test and Mann-Whitney U test.

Results: Twenty-two families, with 15 (68.2%) COVID-19 and 7 (31.8%) non-COVID-19 febrile seizures participated in the study. A substantial proportion of children from both groups were delayed in various developmental domains (13.6-27.3%), with 9 (40.9%) delayed in 2 or more domains and 2 (9.1%) experienced emotional behavioural difficulties. Children with COVID-19 febrile seizures were not more likely to have developmental delay and emotional/behavioural difficulties.

Conclusions: Children with COVID-19 febrile seizures were not at greater risk of developmental delay or emotional/behavioural difficulties. Further longitudinal studies with a larger sample size are warranted.

KEYWORDS:
Emotion behaviour; child development; COVID-19; febrile seizures

INTRODUCTION

Febrile seizures are the most common seizure in childhood, with an approximately 5% incidence rate that peaks in children 12-18 months of age. Febrile seizures are strongly associated with viral respiratory tract infections, with influenza, adenovirus and parainfluenza viruses among the few common causative viruses. During the COVID-19 pandemic, a surge of febrile seizures associated with SARS-CoV-2 infection was observed, particularly during the Omicron wave in early 2022.[1] The incidence of febrile seizures in children during that period rose significantly from 1.7% during the pre-Omicron era to 14.6%, prompting concerns of potential consequences. Existing evidence has shown that febrile seizures are benign and have favourable outcomes. A population-based study in the UK found no differences observed in the academic, intellectual and behaviour outcomes of 10-year-old children with prior febrile seizures compared to healthy peers.[2] Other studies have similarly shown that children with simple or first febrile seizure did not pose greater developmental and behavioural consequences.[3,4] However, the emergence of COVID-19 infection presenting with febrile seizures raises questions about its benign nature.

COVID-19 has been reported to be associated with adverse neurological outcomes in adults, such as brain fog, memory loss, cognitive deficits, gray matter loss, and brain size shrinkage.5 In children, evidence of chronic neurocognitive symptoms and long-term neurodevelopmental sequelae following COVID-19 infection is less clear.[6] Several studies have shown that children also experience ongoing COVID symptoms and are more frequently to report mental health symptoms.[7,8] Others have opposed, reporting no difference in the frequency of reported post-COVID symptoms among test-positive SARS-CoV-2 infection and control.[9] It is postulated that the impact on children is less apparent, as long-term effects may be mild and not severe enough to warrant a visit to the doctor. The neuropsychological symptoms may also be missed and not captured in parent-reported, or healthcare-provider visit surveys.[10,11] Nevertheless, given the limited studies among children, the potential impact of COVID-19 infection on a child's development cannot be dismissed.[12]

This study similarly sought to enhance the understanding of the long-term developmental consequences of COVID-19 in children. In comparison to previous COVID-19 outcome studies, we focused on children presenting with febrile seizures during an acute infection.8-10 We hypothesised that children with COVID-19 infection presenting with more severe presentation such as febrile seizures have poorer neurodevelopmental outcomes compared to their peers with non-COVID-19 febrile seizures. Therefore, the study aimed to compare the developmental and emotional/behavioural outcomes of children with and without COVID-19 presenting with febrile seizures.

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MATERIALS AND METHODS

Participants

This is a cross-sectional study that recruited children, 18-36 months of age, who were previously hospitalised for febrile seizure at Hospital Tuanku Ja'afar, from January to April 2022. The selection period represents the peak of COVID-19, Omicron incidence among children in Malaysia. We excluded children suspected or diagnosed with neurological or neurodevelopmental disorders, central nervous system infection and children whose COVID-19 infection status was unclear, as further described below. All potential families were contacted via a phone call and parents who agreed were provided an appointment for assessment, 9 to 18 months following the initial hospitalisation. Further information about the study and its procedure was explained in detail to parents on the day of assessment and informed consent was obtained from parents who agreed to enrol. Parents completed a structured questionnaire, while the children's development was assessed by a paediatrician through clinical evaluation. This study was approved by the Joint Committee of Research and Ethics of the IMU University, Malaysia (IMU 563-2022) and Ethics Committee of National Malaysia Research Registry (MRR ID-23-00218-ZXO).

Positive COVID-19 case definition

All hospitalised children with febrile seizures and respiratory symptoms were screened for COVID-19 using antigen detection tests from a nasopharyngeal aspirate as part of the local hospital's policy. A positive rapid antigen detection test result indicates a confirmed COVID-19 case, while a negative result indicates a COVID-19-negative case. We excluded children with febrile seizures who tested negative for COVID-19 but had exposure to a household member with COVID-19 in the preceding 2 weeks before hospitalisation. Additionally, children with evidence of COVID-19 and coinfection, such as positive blood cultures or the presence of other viral pathogens such as respiratory syncytial virus (RSV), influenza A, influenza B, adenovirus, parainfluenza types 1-3 and human metapneumovirus (hMPV) were also excluded.

Measures

The questionnaires distributed to parents include demographic information, existing medical conditions and an emotion/behaviour questionnaire, while additional details of the seizure events were retrieved from medical records. The children's developmental milestones were assessed by a paediatrician who was familiar with the developmental tool and who was not directly involved in their prior treatment. A prior training session was held among the four paediatricians involved, to ensure standardisation of its administration, with adjustments to the local cultural context, particularly in the speech and language domains.

Developmental Outcomes

The Schedule of Growing Skills II (SGS-II) is a developmental screening tool for children aged from birth to five years.[13] It provides a rapid and reliable measure of a child's development through the clinician's assessment of 8 skill domains: posture/ locomotor, manipulative, visual, hearing and language, speech and language, interactive, self-care and cognition. The administration of the guided activities in each subscale would take approximately 20 minutes. The number of successfully completed items will be transferred to the SGS II profile form to obtain the equivalent developmental age for that subscale. The scoring and interpretation of the assessment are based on the developmental quotient (DQ) for each skill area calculated as a ratio of the developmental age (DA) divided by the chronological age (CA) and multiplied by 100.13 DQ (%) = DA / CA x 100) DA is derived from the number of successfully completed items in each skill area and converted using the scoring sheet. DQ cut-off point of DQ < 80 for 0–24-month-old children and DQ < 85 for older than 24 months indicates positive developmental concern. The levels have been shown to be accurate in providing the maximum sensitivity and specificity levels (both more than 0.70.[14] The SGS 2 tool was standardised in the UK, which showed good psychometric properties. The test is validated, reporting an excellent correlation (0.87, $p<0.001$) with Denver Developmental Assessment (DDA), with Cronbach's Alpha reliability analysis of 0.86-0.98, and has been used in a similar study population.[15,16]

Emotion/Behaviour Outcomes

The Strengths and Difficulties Questionnaire (SDQ) is a 25-item parent rating screening measure designed to identify behavioural and emotional problems in children.[17] The instrument comprises of five subscales: conduct problems (e.g., fights with others, well-behaved), hyperactivity (e.g., restless, easily distracted), emotional symptoms (e.g., many worries, often unhappy), peer problems (e.g., picked on or bullied, liked by other children) and prosocial behaviour (e.g., considerate of other people's feelings, shares with other children). Each subscale contains 5 items. Each item is rated on a 3-point response scale from 0= 'not true' to 1= 'somewhat true' and 2= 'certainly true'. Scores from each domain (excluding prosocial behaviour) were summed to generate the 'total difficulties score'. The results score ranges from 0 to 40 with the cut-off scores (17-40) for the 'abnormal' category corresponding to the 90th percentiles. Therefore, total difficulties scores falling in the top 10% of scores based on UK normative population norms are indicative of significant emotional/behavioural difficulties (EBD).[18-19] For each subscale, the scores range from 0 to 10 and scores above the cut-off scores represent clinically significant behaviour. Parents were provided with the questionnaire in both languages; the original English questionnaire and the Malay translated version which are readily available on their official website, Youth in Mind 2022.[19] The parent-rated questionnaires are widely used and have shown acceptable reliability and validity.[209]

Statistical analysis

The data was analysed using Microsoft Excel and SPSS Statistic Package 26. We presented the participant characteristics and outcome measures using medians with interquartile range (IQR) for continuous variables and frequency with percentages for categorical variables. Fisher's exact test and Mann-Whitney U test were utilised to compare outcome measures; developmental quotient and emotion/behaviour scores, between children with COVID-19 febrile seizures and non-COVID-19 febrile seizures. A p-value of <0.05 was deemed statistically significant.

Table I: Characteristics of children with febrile seizures, according to COVID-19 status

	All (N=22)	COVID-19	
		Positive (n=15)	Negative (n=7)
Demographic			
Age at assessment, median (IQR) months	31.0 (5.8)	31.0 (7.0)	31.0 (4.0)
Gender, Female, n (%)	8 (36.4)	10 (66.7)	4 (57.1)
Race, Malay, n (%)	17 (77.3)	12 (80.0)	5 (71.4)
Source of information, n (%)			
Mother	18 (81.8)	13 (86.7)	5 (71.4)
Father	4 (18.2)	2 (13.3)	2 (28.6)
Parent age, median (IQR), years	32.2 (3.78)	31.0 (3.0)	35.0 (9.0)
Parent highest education level			
Primary/ Secondary	12 (54.5)	7 (46.7)	5 (71.4)
College/University	10 (45.5)	8 (53.3)	2 (28.6)
Seizure characteristics, n (%) *			
Age at febrile seizure, median (IQR) months	20.0 (5.8)	21.0 (9.0)	19.0(6.0)
Febrile seizure type			
Simple	17 (77.3)	11 (73.3)	6 (85.7)
Complex	5 (22.7)	4(26.7)	1 (14.3)
Seizure episode			
First **	16 (72.7)	13(86.7)	3 (42.9)
≥ 2	6 (27.3)	2 (13.3)	4 (57.1)
Medical/ Birth History, n (%)			
Family history of febrile seizure	5 (22.7)	2 (13.3)	3 (42.9)
Family history of epilepsy	1 (4.5)	1 (6.7)	0
Subsequent febrile seizure event[†]	17 (77.3)	11 (73.3)	6 (85.7)
Pre-existing health conditions[#]	3 (13.6)	3 (20.0)	0
Pregnancy-related issues[†]	8 (36.4)	5 (33.3)	3 (42.9)

*Febrile seizure during the selection period from January till April 2022.
[†] After the selection period till the time of assessment.
**p<0.05
Asymptomatic congenital heart defect, cow's milk protein allergy, Cleft lip
[†] Gestational diabetes, anaemia

Table II: The comparison of developmental (DQ) and emotional/behavioural outcomes of children with febrile seizures, according to COVID-19 test results

	Total N (%)	COVID-19				p-value*	p-value**
		Positive		Negative			
		Median scores (IQR)	Development concern (DQ<80 or 85) n (%)	Median scores (IQR)	Development concern (DQ<80 or 85) n (%)		
Developmental Quotient (DQ)							
Locomotor	6 (27.3)	95.0 (26.0)	4 (26.7)	100.0 (26.0)	2 (28.6)	0.944	1.000
Manipulative	3 (13.6)	103.0 (15.0)	1 (6.7)	88.0 (33.0)	2 (28.6)	0.417	0.227
Visual	6 (27.3)	129.0 (69.0)	3 (20.0)	83.0 (36.0)	3 (42.9)	0.066	0.334
Hearing and Language	3 (13.6)	107.1 (32.5)	2 (13.3)	93.8 (14.3)	1 (14.3)	0.072	1.000
Speech and Language	4 (18.2)	100.0 (38.0)	3 (20.0)	106.0 (33.0)	1 (14.3)	0.751	1.000
Interaction social	3 (13.6)	97.0 (23.0)	2 (13.3)	100.0 (25.0)	1 (14.3)	0.777	1.000
Self-care	5 (22.7)	126.0 (74.0)	4 (26.7)	137.0 (67.0)	1 (14.3)	0.944	1.000
Cognition	6 (27.3)	103.0 (31.0)	3 (20.0)	86.0 (29.0)	3 (42.9)	0.066	0.334
		Median scores (IQR)	**Behaviour** concerns (> cut-off) n (%)	**Median** scores (IQR)	**Behaviour** concerns (> cut-off) n (%)	**p value***	**p value****
Emotion/Behaviour Scores							
Total Difficulties	2 (9.1)	9.0 (4.0)	1 (6.7)	8.0 (7.0)	1 (14.3)	0.456	1.000
Emotion	2 (9.1)	1.0 (2.0)	2 (13.3)	2.0 (1.0)	0	0.382	1.000
Conduct	3 (13.6)	2.0 (2.0)	1 (6.7)	4.0 (4.0)	2 (28.6)	0.296	0.227
Hyperactivity	0.0	3.0 (2.0)	0	1.0 (5.0)	0	0.173	-
Peer	8 (36.4)	3.0 (2.0)	7 (46.7)	2.0 (1.0)	1 (14.3)	0.126	0.193
Prosocial	1 (4.5)	8.0 (3.0)	1 (6.7)	8.0 (3.0)	0	0.720	1.000

* p- values derived from Mann-Whitney U test to compare medians between groups.
** p-value derived from Fisher's exact test to compare proportions between groups.

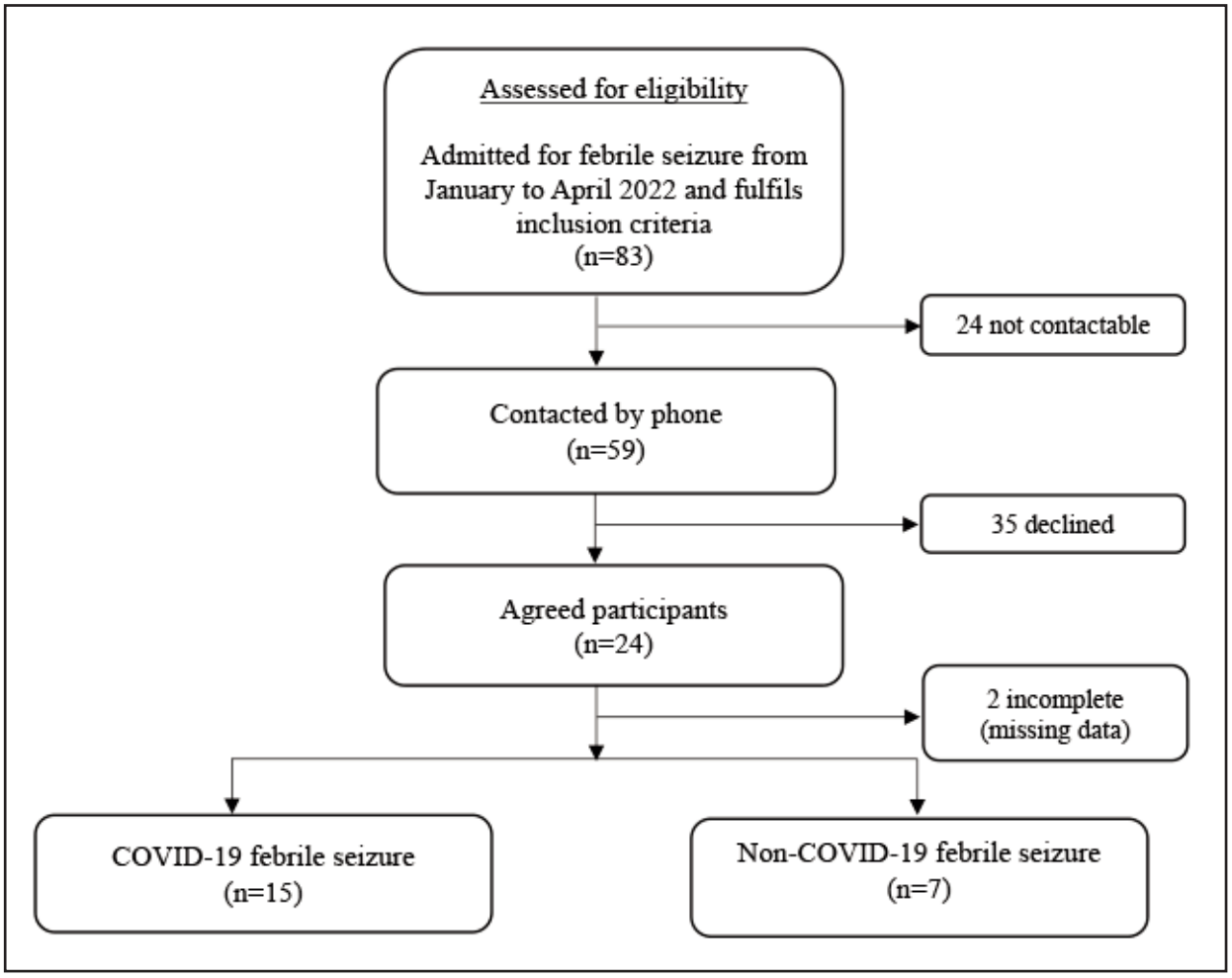

Fig. 1: Flow chart of the participants recruitment to the study

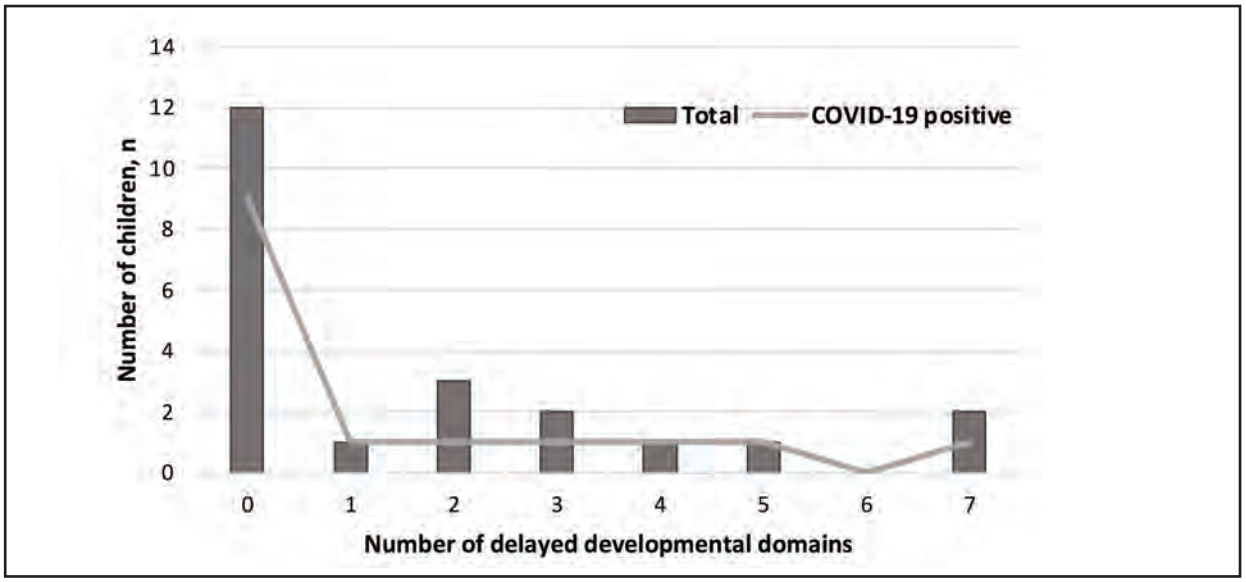

Fig. 2: The number of children according to number of delayed developmental domains

RESULTS

A total of 83 children were admitted for febrile seizure from January to April 2022, of which 24 were not contactable. Among the 59 invited parents, 24 (40.7%) came for their appointments and agreed to participate (Figure I). The final study sample was 22 participants as we excluded two participants with incomplete data. The assessments and data collection were done from November 2022 to July 2023. Compared to study participants, non-participants were of similar age during defined febrile seizure events (median 17.0 (IQR 9) months) and of largely male (65.6%) children.

Table I shows the demographic, seizure characteristics and medical history of the participants. The data was gathered from their accompanying mothers (81.8%) or fathers (18.2%). Among the 22 children, 15 (68.2%) were positive for COVID-19 at the time of the defined febrile seizure. The median age was 31.0 (IQR 5.8) months at the time of assessment and a median age of 20.0 (IQR 5.8) months during their febrile seizure event. The majority were first presentation febrile seizures (16 (72.7%)) and simple seizures (17 (77.3%)). A positive family history of febrile seizure and epilepsy was reported in 5 (22.7%) and 1 (4.5%) child, respectively. None required admission to the intensive care unit (ICU), anti-epileptic prescription, or experienced COVID-19-related complications. Children with COVID-19 febrile seizures were more likely to have first-time febrile seizures (86.7% vs 42.9%, $p < 0.05$). Both groups were otherwise not significantly different in demographic and other medical characteristics.

Figure II illustrates the number of children according to the number of delayed developmental domains. Ten children (45.4%) had developmental delays, with 9 (40.9%) delayed in 2 or more developmental domains. Delays in locomotor, visual and cognition domains were the most common (Table II). The proportion of developmental delays and the median scores for all domains in both groups were not significantly different. (Table II).

The emotion-behaviour scores and proportion of children with emotion-behaviour scores above the cut-off score are displayed in Table II. Two children (9.1%) experienced emotional/behavioural difficulties, with peer problems (8, 36.4%) shown as the predominant symptom. Although peer problems were more commonly reported among children with COVID-19 febrile seizures, the differences in both groups were not statistically significant (46.7% vs 14.3%, p=0.193). The proportion of emotional/behavioural difficulties and the emotion/behaviour median scores of both groups were also not significantly different.

DISCUSSION

Our study observed no differences in the developmental and emotional/behavioural outcomes of children with and without COVID-19 febrile seizures. However, approximately half (45.4%) of the children from both groups were delayed in one or more developmental domains, particularly in the locomotor, visual and cognitive skills. The high numbers in this study exceed pre-pandemic reports of an overall 3.3% developmental delay among children 6-59 months.[21] The results are carefully discussed below, with considerations of the study's limitations.

The association of COVID-19 exposure with early childhood development remains unclear. Studies of infants born to mothers exposed to maternal SARS-CoV-2 infection have reported lower scores in their 8-12 months developmental assessment.[22,23] A study by Jackson et al (2024) of infants exposed to antenatal or neonatal SARS-CoV-2, assessed at 21-32 months of age, showed increased risk of delayed personal-social and social-emotional development as well.[24] However, few studies have shown differing results, demonstrating no risk of developmental delay in all domains during the first 15 months of age.[25,26] As most children with acute COVID-19 infection are usually asymptomatic or experience mild illness, this study focused on outcomes following infection with more severe presentation, specifically febrile seizures. Nevertheless, no association of exposure to COVID-19 infection and developmental delay were demonstrated in this group of children. The effects of COVID-19 infection on brain development in older children may be milder compared to perinatal exposures. Given the limitations of the study, larger sample longitudinal research is still required to substantiate the absence of an association.

Although not the main purpose of the study, our results revealed a high number of developmental delays in this cohort. The findings support the growing evidence of the broader impact of COVID-19 pandemic on early childhood development. A recent study among children below 5 years of age, demonstrated lower scores in their developmental screening assessments in various domains, including communication, problem solving and personal-social compared to pre-pandemic scores.[27] Children born and raised during the pandemic also shown to exhibit lower scores and mental age on the language and communication subscale at 30 months of age compared to pre-pandemic data.[28] The developmental delays are likely attributed to the lack of cognitive stimulation due to restrictions in social activities. Furthermore, parents of children with a history of febrile seizures are likely extra cautious in preventing infection, hence further limiting their children's participation in social events.[29]

The possibility of adverse long-term neurodevelopmental sequelae of febrile seizures should not be disregarded as well.[30] Subtle impairments in cognitive processes, language and behavioural performances, particularly among children with early onset, complex and recurrent febrile seizures have been shown.[4,31,32] Several papers showed delayed vocabulary development, lower developmental scores and lower cognitive function in children with febrile seizures.[4,33] Without a control group in this study, it is difficult to dismiss the potential association between febrile seizure and neurodevelopmental consequences. Lastly, self-selection bias, arising from a higher participation among parents of children with existing developmental concerns, may have also contributed to the elevated detection of developmental delay in this study cohort.

Likewise, emotional/behavioural difficulties was similarly elevated, with our findings showing more than a twofold

increase in peer relationship and conduct problems compared to earlier pre-pandemic study, which reported rates of 9.2% and 5.8%, respectively.[20] A recent local study among preschool children similarly reported higher occurrence of difficulties, reinforcing evidence of the negative impact social isolation has on a child's socioemotional development.[34] Reports of anxiety, fear and depressive symptoms have been described more frequently among children with pre-existing vulnerabilities.[35]

Our study has several limitations that should be considered. First, we encountered a suboptimal participation rate which resulted in a small sample size, limiting both the generalisability of the findings and the statistical power of the study. Second, we employed antigen detection tests to diagnose COVID-19-positive cases. The lack of a more definitive RT-PCR testing may have introduced some diagnostic inaccuracies. However, it is noteworthy that the antigen detection tests had a high positive predictive value during the pandemic's peak, and we meticulously excluded those with negative tests who had close contact with confirmed cases to mitigate this. Third, up to three-quarters of participants experienced recurrent febrile seizures, but the absence of information on their association with COVID-19 infection, presents a confounding factor in assessing the outcomes. The lack of baseline developmental scores and the high selection bias also warrant cautious interpretation of the results.

CONCLUSION

The study did not demonstrate a greater risk of developmental delay or emotional behavioural difficulties among children with COVID-19 febrile seizures. Before dismissing the potential association between COVID-19 and childhood development, a longitudinal population cohort study that addresses the shortcomings of this study is imperative.

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