



Impact of COVID-19 pandemic on neurodevelopmental outcomes of premature infants: a retrospective national cohort study

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ABSTRACT

Objective To compare the neurodevelopmental outcomes of preterm infants before and during the COVID-19 pandemic.

Design Premature infants born in 2018 were assigned to the pre-pandemic group, while those born in 2019 were assigned to the during-pandemic group.

Setting Nationwide cohort study.

Patients Very low birthweight premature infants registered in the Taiwan Premature Infant Follow-up Network database.

Interventions Anti-epidemic measures, including quarantine and isolation protocols, social distancing, the closure of public spaces and restrictions on travel and gatherings during COVID-19 pandemic.

Main outcome measures Outcomes were measured by Bayley Scales of Infant and Toddler Development Third Edition at corrected ages of 6, 12 and 24 months old. Generalised estimating equation (GEE) was applied to incorporate all measurements into a single model.

Results Among the 1939 premature infants who were enrolled, 985 developed before the pandemic, while 954 developed during the pandemic. Premature infants whose development occurred during the pandemic exhibited better cognitive composite at the corrected age of 6 months (beta=2.358; 95% CI, 1.07 to 3.65; p<0.001), and motor composite at corrected ages of 12 months (beta=1.680; 95% CI, 0.34 to 3.02; p=0.014). GEE analysis showed that infants who had grown during the pandemic achieved higher scores in cognitive composite (beta=1.416; 95% CI, 0.36 to 2.48; p=0.009).

Conclusion Premature infants in Taiwan who developed during the pandemic showed better neurodevelopment compared with those born before the pandemic.

INTRODUCTION

The WHO declared COVID-19 a Public Health Emergency of International Concern in January 2020. The virus that causes COVID-19, that is, SARS-CoV-2, rapidly spread worldwide and was declared a pandemic. As of 31 January 2022, there was a cumulative total of 349 641 119 confirmed cases and 5 592 266 deaths globally.¹ In the case of Taiwan,

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Research has suggested that newborns born during the COVID-19 pandemic may experience poorer neurological development.

WHAT THIS STUDY ADDS

⇒ Premature infants developed during the pandemic exhibited improved cognitive and language developmental outcomes in Taiwan.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Despite experiencing the same pandemic, the neurological outcomes of premature infants vary across different social and cultural contexts.

between 2020 and 2021, the nation accumulated a total of 17 050 confirmed cases and 850 recorded fatalities.² The government thus implemented a range of anti-epidemic measures, including quarantine and isolation protocols, social distancing, the closure of public spaces and restrictions on travel and gatherings.^{3 4} These measures have resulted in heightened economic and psychological pressures on caregivers, potentially impacting their capacity to provide high-quality care for children.^{5 6} Infants during the pandemic experienced a reduction in opportunities for interactions beyond their immediate family, and prolonged periods spent at home have contributed to decreased levels of physical activity and increased screen time.⁷ Furthermore, the long-term implementation of isolation policies and the strain on healthcare resources may have led to limited access to medical services.^{8 9} These adverse circumstances have the potential to pose a threat to the neurodevelopment of infants, particularly those born prematurely or with low birth weight, as they are at a heightened risk of

developmental delays.¹⁰ Consequently, investigating the impact of these adverse factors on the early-life neurodevelopment of infants has become a topic of significant interest.

The prevailing evidence consistently indicates that the COVID-19 pandemic has had adverse effects on the neurodevelopment of infants.^{11–15} However, these studies primarily focused on the general population of newborns and did not specifically analyse the impact on preterm infants. Hence, the main objective of this study was to compare the neurodevelopmental outcomes of preterm infants before and during the COVID-19 pandemic from a nationwide perspective in Taiwan.

MATERIALS AND METHODS

Database sources

This research study used data from the Premature Baby Foundation of Taiwan. The Taiwan Premature Infant Follow-up Network (TPFN), managed by this foundation, has collaborated with multiple hospitals in Taiwan since 1995 to document the health conditions of very low birth-weight infants during their hospitalisation and track their neurological development to toddler age. This project covered approximately 80% of very low and extremely low birthweight preterm infants in Taiwan. To ensure patient privacy, all identifiable information was removed from the data before uploading to TPFN.

Study population

All preterm infants with a birth weight of <1500 g, born between the years 2018 and 2019, and followed up in the database were included in the study. Infants born in 2018 were categorised as the pre-pandemic group, while those born in 2019 or after were categorised as the during-pandemic group because their growth occurred in the pandemic era. Exclusion criteria included full-term infants (≥ 37 weeks), cases of mortality and infants with congenital or chromosomal abnormalities.

Outcome measurements

The foundation and collaborating hospitals conducted outpatient follow-up for these preterm infants at corrected ages of 6 months, 12 months, 24 months and 60 months to monitor their health status. The assessment tool used in this study was the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III), which was published in 2006. It evaluates the development of infants and young children from 1 to 42 months of age across five domains: cognition, motor skills, language, socio-emotional functioning and adaptive behaviour.¹⁶ The reliability and validity of the BSID-III assessment tool have been examined and confirmed in studies conducted in Taiwan.¹⁷

Covariates

To address potential confounding factors, the study collected baseline demographic data, including birth

body weight, gestational age, gender, 5 min Apgar score, maternal age, multi-pregnancy and parity. Additionally, major complications in pregnancy, including pre-eclampsia and chorioamnionitis, and major complications in preterm infants, such as respiratory distress syndrome (RDS) requiring surfactant treatment, hemodynamically significant patent ductus arteriosus (PDA) requiring surgical treatment, stage II or higher necrotising enterocolitis (NEC), bronchopulmonary dysplasia (BPD), stage III or higher intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL), were recorded and adjusted for in the analysis.

Statistical analysis

The data retrieval and analysis were conducted using the SAS statistical package (V.9.4; SAS Institute). Demographic data and BSID-III scores were presented as counts with percentages or means with SD. Categorical data were analysed using Pearson's χ^2 test, while continuous variables were compared using the independent t-test. Multiple linear regression models were employed to control for potential confounding factors during BSID-III scores analysis. Generalised estimating equations (GEEs) were used to analyse repetitive measurement of cognitive outcomes at 6, 12 and 24 months old. Statistical significance was set at a p value of <0.05.

RESULTS

Demographic characteristics

During the study period, a total of 2362 preterm infants were enrolled by TPFN. After excluding full-term infants (≥ 37 weeks), cases of mortality and infants with congenital or chromosomal abnormalities, a total of 1939 infants were included in the analysis, with 985 in the pre-pandemic group and 954 in the during-pandemic group. The demographic characteristics of the infants are summarised in [table 1](#). The during pandemic group had a higher proportion of infants with a birth weight below 1 kg (32.99% vs 37.32%, $p=0.05$) and a higher proportion of primipara (60.20% vs 66.88%, $p=0.002$). However, there were no significant differences in terms of gender (male, 51.98% vs 51.15%, $p=0.71$), 1 min Apgar score (mean, 5.97 vs 5.98, $p=0.92$), 5 min Apgar score (mean, 7.86 vs 7.91, $p=0.49$), maternal age (>35 years, 45.89% vs 47.06%, $p=0.60$), gestational age (mean, 29.29 vs 29.29, $p=0.95$), multi-pregnancy (32.18% vs 33.02%, $p=0.69$), pre-eclampsia (24.77% vs 26.73%, $p=0.32$) and chorioamnionitis (5.38% vs 4.09%, $p=0.18$). In terms of complications among preterm infants, the during-pandemic group showed a slight decrease in the incidence of BPD, but the difference was not statistically significant (41.52% vs 37.74%, $p=0.08$). No significant differences were observed in other complications such as RDS (surfactant treatment required, 32.39% vs 30.88%, $p=0.75$), PDA (surgical treatment required, 13.40% vs 13.10%, $p=0.84$), NEC (stage II or III, 5.38% vs 4.72%, $p=0.50$), IVH (stage

Table 1 Characteristics of neonates

Characteristics	Pre-pandemic (n=985)	During-pandemic (n=954)	P value
	n (%)	n (%)	
Gender (males)	512 (51.98)	488 (51.15)	0.71
Birth body weight ≤ 1000 g	325 (32.99)	356 (37.32)	0.05
Maternal age ≥ 35 years	452 (45.89)	448 (47.06)	0.60
Multi-pregnancy	317 (32.18)	315 (33.02)	0.69
Pre-eclampsia	244 (24.77)	255 (26.73)	0.32
Chorioamnionitis	53 (5.38)	39 (4.09)	0.18
Primipara	593 (60.20)	638 (66.88)	0.002
PDA required surgical treatment	132 (13.40)	125 (13.10)	0.84
NEC stage II or III	53 (5.38)	45 (4.72)	0.50
RDS required surfactant	319 (32.39)	294 (30.88)	0.75
BPD	409 (41.52)	360 (37.74)	0.08
IVH stage III and above	54 (5.48)	54 (5.66)	0.86
PVL	47 (4.77)	43 (4.51)	0.78
	Mean\pmSD	Mean\pmSD	P value
Gestational age	29.29 \pm 2.84	29.29 \pm 2.98	0.95
Apgar score			
1 min	5.97 \pm 1.89	5.98 \pm 2.01	0.92
5 min	7.86 \pm 1.49	7.91 \pm 1.55	0.49

BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome.

III and above, 5.48% vs 5.66%, $p=0.86$) and PVL (4.77% vs 4.51%, $p=0.78$).

BSID-III scores before and during COVID-19 pandemic

The Bayley scale scores at 6 months, 12 months and 24 months before and during the pandemic are presented in [table 2](#). Some cases might not have been able to complete all three assessments at the same time point, leading to inconsistent enrollment numbers for different composites.

Furthermore, some cases did not participate in subsequent follow-up assessments, resulting in a reduced number of cases for the 12-month and 24-month assessments. Based on the crude rate analysis, premature infants that developed in the pandemic era had better cognitive (96.54 vs 98.75, $p<0.001$) and language (96.00 vs 97.26, $p=0.02$) outcomes at the corrected age of 6 months. Additionally, at 12 months of corrected age, premature infants that developed during the

Table 2 Results of Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)

Age	Pre-pandemic	During-pandemic	P value
	Mean \pm SD	Mean \pm SD	
6 months old			
Cognitive composite score (n=1860)	96.54 \pm 14.31	98.75 \pm 12.38	<0.001
Language composite score (n=1791)	96.00 \pm 11.54	97.26 \pm 11.21	0.02
Motor composite score (n=1859)	92.76 \pm 16.31	93.61 \pm 15.80	0.25
12 months old			
Cognitive composite score (n=1781)	97.89 \pm 13.50	99.04 \pm 12.18	0.06
Language composite score (n=1716)	91.97 \pm 11.94	92.84 \pm 11.62	0.12
Motor composite score (n=1780)	92.33 \pm 15.05	93.91 \pm 13.88	0.02
24 months old			
Cognitive composite score (n=1683)	93.15 \pm 14.47	94.08 \pm 14.24	0.18
Language composite score (n=1683)	85.89 \pm 24.39	87.35 \pm 21.63	0.19
Motor composite score (n=1683)	91.46 \pm 15.07	91.64 \pm 14.00	0.80

Table 3 Multiple linear regression model on Bayley Scales of Infant Development before and during the pandemic*

Age	Beta	95% CI	P value
6 months old			
Cognitive composite score (n=1578)	2.358	1.07 to 3.65	<0.001
Language composite score (n=1513)	1.059	−0.06 to 2.18	0.06
Motor composite score (n=1577)	0.900	−0.64 to 2.44	0.25
12 months old			
Cognitive composite score (n=1515)	1.054	−0.18 to 2.28	0.09
Language composite score (n=1452)	0.186	−0.97 to 1.34	0.75
Motor composite score (n=1514)	1.680	0.34 to 3.02	0.014
24 months old			
Cognitive composite score (n=1432)	0.707	−0.71 to 2.12	0.32
Language composite score (n=1432)	0.911	−1.51 to 3.33	0.46
Motor composite score (n=1432)	0.184	−1.21 to 1.58	0.79

*Adjusted for birth body weight, gestation age, gender, mother's age, multi-pregnancy, pre-eclampsia, chorioamnionitis, parity, 5 min Apgar score and complications of premature infant.

pandemic era also demonstrated better motor skills (92.33 vs 93.91, $p=0.02$).

Multiple linear regression model for controlling confounding factors

To control for potential confounding factors, we adjusted for birth body weight, gestation age, gender, mother's age, multi-pregnancy, pre-eclampsia, chorioamnionitis, parity, 5 min Apgar score and complications of preterm birth by multiple linear regression models, as presented in [table 3](#). Premature infants that developed during the pandemic demonstrated better cognitive (beta=2.358; 95% CI, 1.07 to 3.65; $p<0.001$) outcomes at the corrected age of 6 months. They also had better motor skills (beta=1.680; 95% CI, 0.34 to 3.02; $p=0.014$) at the corrected age of 12 months.

Analysing repetitive measurement of cognitive outcomes by GEE models

To address the challenge of repetitive measurements for neurodevelopmental outcomes in each infant, we further incorporated all of the outcome measurements into a single model using GEEs. The infants that developed during the pandemic still had higher scores in the cognitive (beta=1.416; 95% CI, 0.36 to 2.48; $p=0.009$) composite ([table 4](#)).

DISCUSSION

This nationwide cohort study revealed that premature infants reared during the pandemic era demonstrated enhanced neurodevelopmental outcomes, particularly in the realms of cognitive and linguistic abilities. The study included more than 80% of very low birthweight preterm infants in Taiwan, ensuring a high level of representativeness. Another noteworthy aspect of this research was the remarkably high rate of cases that completed all three rounds of follow-up assessments, which demonstrates the robustness of the findings. At the time of writing, this investigation was the world's first comprehensive national study focusing on the developmental differences among preterm infants before and during the pandemic. In contrast to prior studies, which predominantly conducted single-time-point analyses,¹³ our study employed GEE to integrate data from three time points and effectively addressed the issue of repeated measurements.

Infant neurodevelopment is influenced by a variety of factors, such as genetic conditions,¹⁸ maternal mental health during pregnancy,^{19 20} prematurity,^{21 22} intra-uterine and neonatal insults,²³ perinatal infection or inflammation,^{24 25} socioeconomic status^{26 27} and caregivers' education level.²⁸ Considering the current lack of evidence regarding the influence of SARS-CoV-2 on placental function, fetal inflammatory response or

Table 4 Generalised estimating equations of the Bayley Scales of Infant Development before and during the pandemic*

	Beta	95% CI	P value
Bayley Scales of Infant Development			
Cognitive composite score (n=4525)	1.416	0.36 to 2.48	0.009
Language composite score (n=4397)	0.892	−0.39 to 2.18	0.17
Motor composite score (n=4523)	0.899	−0.29 to 2.09	0.13

*Adjusted for birth body weight, gestation age, gender, mother's age, multi-pregnancy, pre-eclampsia, chorioamnionitis, parity, 5 min Apgar score and complications of premature infant.

vertical transmission between mother and child, the primary factors affecting neurodevelopment are likely postnatal environmental factors.^{29 30}

In relevant studies, Huang *et al* employed the Gesell Developmental Schedules as an assessment tool and discovered that the experience of the pandemic in 2020 was linked to a heightened risk of delays in the fine motor and communication composite at 12 months of age. Furthermore, several of the studies mentioned used the Ages & Stages Questionnaire, 3rd Edition as their assessment tool. Huang *et al* found no impact of the pandemic on the development of infants at 6 months of age. Shuffrey *et al* reported that infants born during the pandemic had notably lower scores in the gross motor skills, fine motor skills and personal-social development domains at 6 months of age. Imboden *et al* noted a reduction in problem-solving scores at 6 months of age following the pandemic, but an increase at 24 months of age. Additionally, there was a slight decline in the communication domain at 6 months of age and 12 months of age. Lau *et al* observed trends of lower scores in cognitive and motor development at around 24 months of age. While the conclusions of these studies are not entirely consistent, infants and children born during the pandemic tended to have poorer developmental outcomes. This observation aligns with findings from Hessami's systematic review and meta-analysis, which indicates a higher likelihood of communication impairment in the pandemic cohort. Possible reasons for this decline include reduced opportunities for social interaction, financial difficulties faced by families, the implementation of mandatory mask-wearing policies and an increased prevalence of mental health issues among caregivers.^{11–15}

However, our study yielded different results, which could be explained by the following. In 2003, Taiwan experienced an outbreak of SARS, which resulted in significant fatalities due to inadequate government policies and a lack of experience in managing large-scale infectious diseases, leading to societal panic.^{31 32} Drawing from this experience, when faced with the COVID-19 pandemic, the public exhibited increased vigilance and a high degree of compliance with preventive measures.^{33 34} Parents in Taiwan may have taken extra precautions to protect their infants, such as reducing outdoor activities to prevent potential infections, or paying special attention to their infants' health status. Moreover, restriction of social interactions might have further increased the amount of time parents were able to spend with their infant. These actions could have enhanced the parent-infant bond, potentially contributing to the observed positive effects on infant development. Moreover, compared with most countries worldwide that experienced an economic downturn during the pandemic, Taiwan's economy remained relatively stable.^{35–37} This potentially suggests that a smaller number of families in Taiwan encountered economic challenges or instability, which may have had a positive impact on childcare. The possible underlying mechanism may be related to the

developmental origins of health and disease theory. It is hypothesised that certain environmental stressful events interact with DNA and hormones, potentially impacting brain development and function.^{38 39} However, how this mechanism influences development under protective conditions remains to be studied in the future.

Additionally, our statistical analysis revealed that the most substantial developmental differences were observed at 6 months of age, while no significant differences were noted at 24 months of age. This may imply that the impact of the pandemic was primarily limited to the early stages of life and could be temporary. However, further research with long-term follow-up is needed to confirm these observations.

There were some limitations in this study. Preterm infants with a birth weight exceeding 1500 g were not included in the TPFN programme. Due to the stringent privacy protection policy of TPFN, we also lacked data on caregiver education levels, socioeconomic status, whether they live in urban or rural areas, and whether the infants themselves had COVID-19, which could all be related to development. The major outbreak of the pandemic in Taiwan occurred after April 2022. However, TPFN currently only provides data up to the end of 2021. Therefore, we are unable to analyse the pandemic situation in Taiwan after 2022. The data from TPFN did not categorise the severity of PVL. Therefore, our analysis is based solely on the presence or absence of PVL.

CONCLUSION

Premature infants with very low birth weight whose development occurred during the pandemic in Taiwan showed improved neurodevelopmental outcomes compared with their pre-pandemic counterparts.

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Contributors T-CT conceptualised and designed the study, carried out the statistical analyses, drafted and revised the manuscript. T-MW, Y-CH and C-TH conceptualised the study and reviewed the manuscript. Y-HL carried out the statistical analyses and reviewed the manuscript. M-CL conceptualised the study, supervised data collection, carried out analyses, reviewed the manuscript and coordinated the study. M-CL is responsible for the overall content as guarantor. The guarantor accepts full responsibility for the finished work and the conduct of the study, had access to the data, and controlled the decision to publish.

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