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Impact of COVID-19 Pandemic on Neurodevelopmental Outcomes of Premature Infants: a retrospective national cohort study

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Title: Impact of COVID-19 Pandemic on Neurodevelopmental Outcomes of Premature Infants: a retrospective national cohort study

Running Title: COVID-19 and Neurodevelopment of Preemie

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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: National wide cohort study

Patients: Very low birth weight premature infants registered in the Taiwan Premature Infant Follow-up Network (TPFN) 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 (BDIS-III) at corrected age of 6, 12, and 24 months old. Generalized estimating equation (GEE) was applied to incorporate all measurements into a single model.

Results: Among the 1,939 premature infants who were enrolled, 985 developed before the pandemic, while 954 developed the pandemic. Premature infants whose development occurred during the pandemic exhibited better cognitive (beta = 2.388; 95% CI, 1.21 to 3.57) and language (beta = 1.306; 95% CI, 0.27 to 2.34) outcomes at the corrected age of 6 months, and improved motor skills at corrected ages of 12 months (beta = 1.529; 95% CI, 0.30-2.76). GEE analysis showed that infants who had grown during the pandemic achieved higher scores in both cognitive (beta = 1.487; 95% CI, 0.53-2.44) and language composite (beta = 1.336; 95% CI, 0.19-2.48).

Conclusion: Premature infants in Taiwan who developed during the pandemic showed better cognitive and language development compared to those born before the pandemic.

What is already known on this topic: Researches have 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.

K E Y W O R D S: Premature infants, Neurodevelopment, COVID-19, Cohort study

Introduction

The World Health Organization declared coronavirus 2019 (COVID-19) a Public Health Emergency of International Concern in January 2020. The virus that causes COVID-19, i.e., SARS-CoV-2, rapidly spread worldwide and was declared a pandemic. As of January 31, 2022, there was a cumulative total of 349,641,119 confirmed cases and 5,592,266 deaths globally.[1] In the case of Taiwan, 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 focussed on the general population of newborns and did not specifically analyze 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 utilized 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 hospitalization and track their neurological development to toddler age. This project covered approximately 80% of very low and extremely low birth weight preterm infants in Taiwan. To ensure patient privacy, all identifiable information was removed from the data before uploading to TPFN. The study protocol was approved by the institutional review board of Taichung Veterans General Hospital and TPFN, and the requirement for informed consent was waived.

Study population

All preterm infants with a birth weight less than 1500g, born between the years 2018 and 2019, and followed up in the database were included in the study. Infants born in 2018 were categorized as the pre-pandemic group, while those born in 2019 or after were categorized 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 (BDIS-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 behavior.[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, sex, maternal age, and parity. Additionally, major complications in preterm infants, such as hemodynamically significant patent ductus arteriosus (PDA) requiring surgical treatment, stage II or higher necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), stage III or higher intraventricular hemorrhage (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 (version 9.4; SAS Institute, Cary, North Carolina, USA). Demographic data and BSID-III scores were presented as counts with percentages or means with standard deviation. Categorical data were analyzed using Pearson's Chi-square 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. Generalized Estimating Equations were used to analyze repetitive measurement of cognitive outcomes at 6, 12, and 24 months old. Statistical significance was set at a *p*-value of less than 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 summarized in Table 1. The during-pandemic group had a higher proportion of infants with a birth weight below one kilogram (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%, $P = 0.71$), maternal age (>35 years, 45.89% vs 47.06%, $P = 0.60$), or gestational age (mean, 29.29 vs 29.29, $P = 0.95$). 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 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 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 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, gestational age, sex, maternal age, parity, and complications of preterm birth by multiple linear regression models, as presented in Table 3. The findings are consistent with the crude rate analysis. Premature infants that developed during the pandemic demonstrated better cognitive (beta = 2.388; 95% CI, 1.21 to 3.57; P <0.001) and language (beta = 1.306; 95% CI, 0.27 to 2.34; P = 0.01) outcomes at the corrected age of 6 months. They also had better motor skills (beta = 1.529; 95% CI, 0.30-2.76; P = 0.01) at the corrected age of 12 months.

Analyzing repetitive measurement of cognitive outcomes by generalized estimating equations (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 generalized estimating equations (GEE). The infants that developed during the pandemic still had higher scores in the cognitive (beta = 1.487; 95% CI, 0.53-2.44; P = 0.002) and language composite (beta = 1.336; 95% CI, 0.19-2.48; P = 0.02). (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 birth weight 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 the world's first comprehensive national study focusing on the developmental differences among preterm infants before and after the pandemic. In contrast to prior studies, which predominantly conducted single-time-point analyses,[13] our study employed Generalized Estimating Equations (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, prematurity,[19,20] intrauterine and neonatal insults,[21] perinatal infection or inflammation,[22,23] socioeconomic status,[24,25] and caregivers' education level.[26] Considering the current lack of evidence regarding the influence of SARS-CoV-2 on placental function, fetal inflammatory response, or vertical transmission between mother and child, the primary factors affecting neurodevelopment are likely postnatal environmental factors.[27,28]

In relevant studies, Huang et al. employed the Gesell Developmental Schedules (GDS) 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 (ASQ-3) 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 Severe Acute Respiratory Syndrome (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.[29,30] 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.[31,32] 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 to most countries worldwide that experienced an economic downturn during the pandemic, Taiwan's economy remained relatively stable.[33-35] 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.

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 grams were not included in the TPFN program. We also lacked data on caregiver education levels, socioeconomic status, and whether the infants themselves had COVID-19, which could all be related to development.

Conclusion

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

Declaration of competing interest

The authors declare there are no conflicts of interest to disclose.

Funding

No funding was received in this study.

Ethics approval status

The study protocol was approved by the institutional review board of Taichung Veterans General Hospital and TPFN, and the requirement for informed consent was waived. (ID: CE22352B)

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Table 1. Characteristics of neonates

Characteristics	pre-pandemic (n=985)	during-pandemic (n=954)	
	n (%)	n (%)	***P***
Gender (males)	512 (51.98)	488 (51.15)	.71
Birth body weight ≤1000 gm	325 (32.99)	356 (37.32)	.05
Maternal age ≥35 years	452 (45.89)	448 (47.06)	.60
Primipara	593 (60.20)	638 (66.88)	.002
PDA required surgical treatment	132 (13.40)	125 (13.10)	.84
NEC stage II or III	53 (5.38)	45 (4.72)	.50
BPD	409 (41.52)	360 (37.74)	.08
IVH stage III and above	54 (5.48)	54 (5.66)	.86
PVL	47 (4.77)	43 (4.51)	.78
	mean ± SD	mean ± SD	***P***
Gestational age	29.29 ± 2.84	29.29 ± 2.98	.95

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

Age	pre-pandemic mean ± SD	during-pandemic mean ± SD	*P*
6 months old			
cognitive composite score (n = 1860)	96.54 ± 14.31	98.75 ± 12.38	<.001
language composite score (n = 1791)	96.00 ± 11.54	97.26 ± 11.21	.02
motor composite score (n = 1859)	92.76 ± 16.31	93.61 ± 15.80	.25
12 months old			
cognitive composite score (n = 1781)	97.89 ± 13.50	99.04 ± 12.18	.06
language composite score (n = 1716)	91.97 ± 11.94	92.84 ± 11.62	.12
motor composite score (n = 1780)	92.33 ± 15.05	93.91 ± 13.88	.02
24 months old			
cognitive composite score (n = 1683)	93.15 ± 14.47	94.08 ± 14.24	.18
language composite score (n = 1683)	85.89 ± 24.39	87.35 ± 21.63	.19
motor composite score (n = 1683)	91.46 ± 15.07	91.64 ± 14.00	.80

Table 3. Multiple linear regression model on Bayley scales of infant development before and during the pandemic

Age	beta	95% CI	*P*
6 months old			
cognitive composite score (n = 1858)	2.388	1.21-3.57	<.001
language composite score (n = 1789)	1.306	0.27-2.34	.01
motor composite score (n = 1857)	0.928	-0.46-2.31	.18
12 months old			
cognitive composite score (n = 1779)	1.038	-0.10-2.17	.07
language composite score (n = 1714)	0.703	-0.37-1.78	.20
motor composite score (n = 1778)	1.529	0.30-2.76	.01
24 months old			
cognitive composite score (n = 1681)	0.905	-0.37-2.18	.16
language composite score (n = 1681)	1.350	-0.83-3.53	.22
motor composite score (n = 1681)	0.183	-1.06-1.42	.77

* Adjusted for birth body weight, gestation age, sex, mother's age, parity, and complications of premature infant

Table 4. Generalized Estimating Equations of the Bayley scales of infant development before and during the pandemic

	beta	95% CI	*P*
Bayley scales of infant development			
cognitive composite score (n = 5318)	1.487	0.53-2.44	.002
language composite score (n = 5184)	1.336	0.19-2.48	.02
motor composite score (n = 5316)	0.856	-0.21-1.92	.11

* Adjusted for birth body weight, gestation age, sex, mother's age, parity, and complications of premature infant

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Title: Impact of COVID-19 Pandemic on Neurodevelopmental Outcomes of Premature Infants: a retrospective national cohort study

Running Title: COVID-19 and Neurodevelopment of Preemie

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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: National wide cohort study

Patients: Very low birth weight premature infants registered in the Taiwan Premature Infant Follow-up Network (TPFN) 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 (BDIS-III) at corrected age of 6, 12, and 24 months old. Generalized estimating equation (GEE) was applied to incorporate all measurements into a single model.

Results: Among the 1,939 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, 1.07-3.65; $P < 0.001$), and motor composite at corrected ages of 12 months (beta = 1.680; 95% CI, 0.34-3.02; $P = 0.014$). GEE analysis showed that infants who had grown during the pandemic achieved higher scores in cognitive composite (beta = 1.416; 95% CI, 0.36-2.48, $P = 0.009$).

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

What is already known on this topic: Research have 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.

K E Y W O R D S: Premature infants, Neurodevelopment, COVID-19, Cohort study

Introduction

The World Health Organization declared coronavirus 2019 (COVID-19) a Public Health Emergency of International Concern in January 2020. The virus that causes COVID-19, i.e., SARS-CoV-2, rapidly spread worldwide and was declared a pandemic. As of January 31, 2022, there was a cumulative total of 349,641,119 confirmed cases and 5,592,266 deaths globally.[1] In the case of Taiwan, 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 analyze 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 utilized 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 hospitalization and track their neurological development to toddler age. This project covered approximately 80% of very low and extremely low birth weight preterm infants in Taiwan. To ensure patient privacy, all identifiable information was removed from the data before uploading to TPFN. The study protocol was approved by the institutional review board of Taichung Veterans General Hospital and TPFN, and the requirement for informed consent was waived.

Study population

All preterm infants with a birth weight less than 1500g, born between the years 2018 and 2019, and followed up in the database were included in the study. Infants born in 2018 were categorized as the pre-pandemic group, while those born in 2019 or after were categorized 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 (BDIS-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 behavior.[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-minute Apgar score, maternal age, multi-pregnancy, and parity. Additionally, major complications in pregnancy, including preeclampsia 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 necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), stage III or higher intraventricular hemorrhage (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 (version 9.4; SAS Institute, Cary, North Carolina, USA). Demographic data and BSID-III scores were presented as counts with percentages or means with standard deviation. Categorical data were analyzed using Pearson's Chi-square 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. Generalized Estimating Equations were used to analyze repetitive measurement of cognitive outcomes at 6, 12, and 24 months old. Statistical significance was set at a *p*-value of less than 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 summarized in Table 1. The during-pandemic group had a higher proportion of infants with a birth weight below one kilogram (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-minute Apgar score (mean, 5.97 vs 5.98, $P = 0.92$), 5-minute 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%, $P = 0.69$), preeclampsia (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 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 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, preeclampsia, chorioamnionitis, parity, 5-minute 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, 1.07-3.65; $P < 0.001$) outcomes at the corrected age of 6 months. They also had better motor skills (beta = 1.680; 95% CI, 0.34-3.02; $P = 0.014$) at the corrected age of 12 months.

Analyzing repetitive measurement of cognitive outcomes by generalized estimating equations (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 generalized estimating equations (GEE). The infants that developed during the pandemic still had higher scores in the cognitive (beta = 1.416; 95% CI, 0.36-2.48; $P = 0.009$) 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 birth weight 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 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 Generalized Estimating Equations (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] intrauterine 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 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 (GDS) 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 (ASQ-3) 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 Severe Acute Respiratory Syndrome (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 to 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 (DOHaD) theory. It is hypothesized 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 grams were not included in the TPFN program. 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 analyze the pandemic situation in Taiwan after 2022. The data from TPFN did not categorize 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 to their pre-pandemic counterparts.

Declaration of competing interest

The authors declare there are no conflicts of interest to disclose.

Funding

No funding was received in this study.

Ethics approval status

The study protocol was approved by the institutional review board of Taichung Veterans General Hospital and TPFN, and the requirement for informed consent was waived. (ID: CE22352B)

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Contributors

TCT conceptualized and designed the study, carried out the statistical analyses, drafted and revised the manuscript. TMW, YCH, and CTH conceptualized the study and reviewed the manuscript. YHL carried out the statistical analyses and reviewed the manuscript. MCL conceptualized the study, supvervised data collection, carried out analyses, reviewed the manuscript, and coordinated the study.

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Table 1. Characteristics of neonates

Characteristics	pre-pandemic (n=985)	during-pandemic (n=954)	
	n (%)	n (%)	*P*
Gender (males)	512 (51.98)	488 (51.15)	.71
Birth body weight ≤1000 gm	325 (32.99)	356 (37.32)	.05
Maternal age ≥35 years	452 (45.89)	448 (47.06)	.60
Multi-pregnancy	317 (32.18)	315 (33.02)	.69
Preeclampsia	244 (24.77)	255 (26.73)	.32
Chorioamnionitis	53 (5.38)	39 (4.09)	.18
Primipara	593 (60.20)	638 (66.88)	.002
PDA required surgical treatment	132 (13.40)	125 (13.10)	.84
NEC stage II or III	53 (5.38)	45 (4.72)	.50
RDS required surfactant	319 (32.39)	294 (30.88)	.75
BPD	409 (41.52)	360 (37.74)	.08
IVH stage III and above	54 (5.48)	54 (5.66)	.86
PVL	47 (4.77)	43 (4.51)	.78
	mean ± SD	**mean ± SD**	***P***
Gestational age	29.29 ± 2.84	29.29 ± 2.98	.95
Apgar score			
1-minute	5.97 ± 1.89	5.98 ± 2.01	.92
5-minute	7.86 ± 1.49	7.91 ± 1.55	.49

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

Age	pre-pandemic	during-pandemic	
	mean ± SD	mean ± SD	*P*
6 months old			
cognitive composite score (n = 1860)	96.54 ± 14.31	98.75 ± 12.38	<.001
language composite score (n = 1791)	96.00 ± 11.54	97.26 ± 11.21	.02
motor composite score (n = 1859)	92.76 ± 16.31	93.61 ± 15.80	.25
12 months old			
cognitive composite score (n = 1781)	97.89 ± 13.50	99.04 ± 12.18	.06
language composite score (n = 1716)	91.97 ± 11.94	92.84 ± 11.62	.12
motor composite score (n = 1780)	92.33 ± 15.05	93.91 ± 13.88	.02
24 months old			
cognitive composite score (n = 1683)	93.15 ± 14.47	94.08 ± 14.24	.18
language composite score (n = 1683)	85.89 ± 24.39	87.35 ± 21.63	.19
motor composite score (n = 1683)	91.46 ± 15.07	91.64 ± 14.00	.80

Table 3. Multiple linear regression model on Bayley scales of infant development before and during the pandemic*

Age	beta	95% CI	*P*
6 months old			
cognitive composite score (n = 1578)	2.358	1.07-3.65	<.001
language composite score (n = 1513)	1.059	-0.06-2.18	.06
motor composite score (n = 1577)	0.900	-0.64-2.44	.25
12 months old			
cognitive composite score (n = 1515)	1.054	-0.18-2.28	.09
language composite score (n = 1452)	0.186	-0.97-1.34	.75
motor composite score (n = 1514)	1.680	0.34-3.02	.014
24 months old			
cognitive composite score (n = 1432)	0.707	-0.71-2.12	.32
language composite score (n = 1432)	0.911	-1.51-3.33	.46
motor composite score (n = 1432)	0.184	-1.21-1.58	.79

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

Table 4. Generalized Estimating Equations of the Bayley scales of infant development before and during the pandemic*

	beta	95% CI	*P*
Bayley scales of infant development			
cognitive composite score (n = 4525)	1.416	0.36-2.48	.009
language composite score (n = 4397)	0.892	-0.39-2.18	.17
motor composite score (n = 4523)	0.899	-0.29-2.09	.13

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

Title: Impact of COVID-19 Pandemic on Neurodevelopmental Outcomes of Premature Infants: a retrospective national cohort study

Running Title: COVID-19 and Neurodevelopment of Preemie

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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: National wide cohort study

Patients: Very low birth weight premature infants registered in the Taiwan Premature Infant Follow-up Network (TPFN) 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 (BDIS-III) at corrected age of 6, 12, and 24 months old. Generalized estimating equation (GEE) was applied to incorporate all measurements into a single model.

Results: Among the 1,939 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 ~~and language (beta = 1.306; 95% CI, 0.27 to 2.34) outcome~~ at the corrected age of 6 months (beta = 2.358; 95% CI, 1.07-3.65; $P < 0.001$), and ~~improved~~ better motor composite ~~skills~~ at corrected ages of 12 months (beta = 1.680; 95% CI, 0.34-3.02; $P = 0.014$). GEE analysis showed that infants who had grown during the pandemic achieved higher scores in ~~both~~ cognitive ~~(beta = 1.487; 95% CI, 0.53-2.44) and language~~ composite (beta = 1.416; 95% CI, 0.36-2.48, $P = 0.009$).

Conclusion: Premature infants in Taiwan who developed during the pandemic showed better ~~cognitive and language~~ neurodevelopment compared to those born before the pandemic.

What is already known on this topic: Research have 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.

K E Y W O R D S: Premature infants, Neurodevelopment, COVID-19, Cohort study

Introduction

The World Health Organization declared coronavirus 2019 (COVID-19) a Public Health Emergency of International Concern in January 2020. The virus that causes COVID-19, i.e., SARS-CoV-2, rapidly spread worldwide and was declared a pandemic. As of January 31, 2022, there was a cumulative total of 349,641,119 confirmed cases and 5,592,266 deaths globally.[1] In the case of Taiwan, 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 analyze 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 utilized 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 hospitalization and track their neurological development to toddler age. This project covered approximately 80% of very low and extremely low birth weight preterm infants in Taiwan. To ensure patient privacy, all identifiable information was removed from the data before uploading to TPFN. The study protocol was approved by the institutional review board of Taichung Veterans General Hospital and TPFN, and the requirement for informed consent was waived.

Study population

All preterm infants with a birth weight less than 1500g, born between the years 2018 and 2019, and followed up in the database were included in the study. Infants born in 2018 were categorized as the pre-pandemic group, while those born in 2019 or after were categorized 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 (BDIS-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 behavior.[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-minute Apgar score, maternal age, multi-pregnancy, and parity. Additionally, major complications in pregnancy, including preeclampsia 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 necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), stage III or higher intraventricular hemorrhage (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 (version 9.4; SAS Institute, Cary, North Carolina, USA). Demographic data and BSID-III scores were presented as counts with percentages or means with standard deviation. Categorical data were analyzed using Pearson's Chi-square 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. Generalized Estimating Equations were used to analyze repetitive measurement of cognitive outcomes at 6, 12, and 24 months old. Statistical significance was set at a *p*-value of less than 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 summarized in Table 1. The during-pandemic group had a higher proportion of infants with a birth weight below one kilogram (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-minute Apgar score (mean, 5.97 vs 5.98, $p = 0.92$), 5-minute 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%, $P = 0.69$), preeclampsia (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 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 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, preeclampsia, chorioamnionitis, parity, 5-minute Apgar score, and complications of preterm birth by multiple linear regression models, as presented in Table 3. ~~The findings are consistent with the crude rate analysis.~~ Premature infants that developed during the pandemic demonstrated better cognitive (beta = 2.358; 95% CI, 1.07-3.65; $P < 0.001$) outcomes at the corrected age of 6 months. They also had better motor skills (beta = 1.680; 95% CI, 0.34-3.02; $P = 0.014$) at the corrected age of 12 months.

Analyzing repetitive measurement of cognitive outcomes by generalized estimating equations (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 generalized estimating equations (GEE). The infants that developed during the pandemic still had higher scores in the cognitive (beta = 1.416; 95% CI, 0.36-2.48; $P = 0.009$) 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 birth weight 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 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 Generalized Estimating Equations (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] intrauterine 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 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 (GDS) 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 (ASQ-3) 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 Severe Acute Respiratory Syndrome (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 to 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 (DOHaD) theory. It is hypothesized 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 grams were not included in the TPFN program. 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 analyze the pandemic situation in Taiwan after 2022. The data from TPFN did not categorize 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 to their pre-pandemic counterparts.

Declaration of competing interest

The authors declare there are no conflicts of interest to disclose.

Funding

No funding was received in this study.

Ethics approval status

The study protocol was approved by the institutional review board of Taichung Veterans General Hospital and TPFN, and the requirement for informed consent was waived. (ID: CE22352B)

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Contributors

TCT conceptualized and designed the study, carried out the statistical analyses, drafted and revised the manuscript. TMW, YCH, and CTH conceptualized the study and reviewed the manuscript. YHL carried out the statistical analyses and reviewed the manuscript. MCL conceptualized the study, supervised data collection, carried out analyses, reviewed the manuscript, and coordinated the study.

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Table 1. Characteristics of neonates

Characteristics	pre-pandemic (n=985)	during-pandemic (n=954)	
	n (%)	n (%)	*P*
Gender (males)	512 (51.98)	488 (51.15)	.71
Birth body weight ≤1000 gm	325 (32.99)	356 (37.32)	.05
Maternal age ≥35 years	452 (45.89)	448 (47.06)	.60
Multi-pregnancy	317 (32.18)	315 (33.02)	.69
Preeclampsia	244 (24.77)	255 (26.73)	.32
Chorioamnionitis	53 (5.38)	39 (4.09)	.18
Primipara	593 (60.20)	638 (66.88)	.002
PDA required surgical treatment	132 (13.40)	125 (13.10)	.84
NEC stage II or III	53 (5.38)	45 (4.72)	.50
RDS required surfactant	319 (32.39)	294 (30.88)	.75
BPD	409 (41.52)	360 (37.74)	.08
IVH stage III and above	54 (5.48)	54 (5.66)	.86
PVL	47 (4.77)	43 (4.51)	.78
	mean ± SD	mean ± SD	*P*
Gestational age	29.29 ± 2.84	29.29 ± 2.98	.95
Apgar score			
1-minute	5.97 ± 1.89	5.98 ± 2.01	.92
5-minute	7.86 ± 1.49	7.91 ± 1.55	.49

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

Age	pre-pandemic	during-pandemic	
	mean ± SD	mean ± SD	*P*
6 months old			
cognitive composite score (n = 1860)	96.54 ± 14.31	98.75 ± 12.38	<.001
language composite score (n = 1791)	96.00 ± 11.54	97.26 ± 11.21	.02
motor composite score (n = 1859)	92.76 ± 16.31	93.61 ± 15.80	.25
12 months old			
cognitive composite score (n = 1781)	97.89 ± 13.50	99.04 ± 12.18	.06
language composite score (n = 1716)	91.97 ± 11.94	92.84 ± 11.62	.12
motor composite score (n = 1780)	92.33 ± 15.05	93.91 ± 13.88	.02
24 months old			
cognitive composite score (n = 1683)	93.15 ± 14.47	94.08 ± 14.24	.18
language composite score (n = 1683)	85.89 ± 24.39	87.35 ± 21.63	.19
motor composite score (n = 1683)	91.46 ± 15.07	91.64 ± 14.00	.80

Table 3. Multiple linear regression model on Bayley scales of infant development before and during the pandemic*

Age	beta	95% CI	*P*
6 months old			
cognitive composite score (n = 1578)	2.358	1.07-3.65	<.001
language composite score (n = 1513)	1.059	-0.06-2.18	.06
motor composite score (n = 1577)	0.900	-0.64-2.44	.25
12 months old			
cognitive composite score (n = 1515)	1.054	-0.18-2.28	.09
language composite score (n = 1452)	0.186	-0.97-1.34	.75
motor composite score (n = 1514)	1.680	0.34-3.02	.014
24 months old			
cognitive composite score (n = 1432)	0.707	-0.71-2.12	.32
language composite score (n = 1432)	0.911	-1.51-3.33	.46
motor composite score (n = 1432)	0.184	-1.21-1.58	.79

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

Table 4. Generalized Estimating Equations of the Bayley scales of infant development before and during the pandemic*

	beta	95% CI	*P*
Bayley scales of infant development			
cognitive composite score (n = 4525)	1.416	0.36-2.48	.009
language composite score (n = 4397)	0.892	-0.39-2.18	.17
motor composite score (n = 4523)	0.899	-0.29-2.09	.13

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

Dear Editor:

Thank you for inviting us to submit a revised draft of our manuscript entitled, "Impact of COVID-19 Pandemic on Neurodevelopmental Outcomes of Premature Infants: a retrospective national cohort study". We also appreciate the time and effort you and each of the reviewers have dedicated to providing insightful feedback on ways to strengthen our paper. Thus, it is with great pleasure that we resubmit our revised article for further consideration. We have incorporated changes that reflect the detailed suggestions you have graciously provided. We also hope that our edits and the responses we provide below satisfactorily address all the issues and concerns you and the reviewers have noted.

To facilitate your review of our revisions, the following is a point-by-point response to the questions and comments.

To Editor:

1. All references have been checked according to the journal style.

2. ***Comment:*** **Agree with minor revisions, but also a check for language and grammar. This sentence in the Abstract- Results: Among the 1,939 premature infants who were enrolled, 985 developed before the pandemic, while 954 developed (add "during") the pandemic.**

   Answer: We have added “during” in the sentence.

3. ***Comment:*** **Page 11, Line 20: Change “after” to “during”.**

   Answer: It has been changed to “during the pandemic” **(Page 11, Line 22)**

4. ***Comment:*** **Pages 21 & 22: *notes below Tables 3 & 4. ‘*’ is not cited in either Table. Either delete notes or cite as appropriate.**

   Answer: It has been cited in both table 3 and table 4. **(Page 20-21)**

To Reviewer 1, Prof. San-Nan Yang:

Thank you for your comments and suggestions. The questions are answered below:

1. ***Comment:*** **The authors should expand the discussion for the possible transplacental mediators from maternal care-giving protocols, such as breast milk to the offspring. Why such programing pathogenesis can be long-lasting effects, and hence affects in the offspring?**

   Answer: Thank you for reminding us of this point. In our study, all infants were born before the pandemic. Theoretically, our results are less likely to be influenced by transplacental mediators. However, we acknowledge the necessity to explore potential pathogenesis. Therefore, we have added the following paragraph in the **Discussion section**: "The possible underlying mechanism may be related to the developmental origins of health and disease (DOHaD) theory. It is hypothesized that certain environmental stressful events interact with DNA and hormones, potentially impacting brain development and function. However, how this mechanism influences development under protective conditions remains to be studied in the future." **(Page 12, Line 2 - 5)**

2. ***Comment:*** **Is the rationale of family income and urbanization which contribute a role in this study? The authors should discuss these factors.**

   Answer: We acknowledge that family income and urbanization are likely to play a significant role in this study. However, due to the stringent privacy protection policy of TPFN, we are unable to access any background information beyond the health condition of the mother. We have added this issue as a limitation in **Discussion section (Page 12, Line 11 - 13)**.

3. ***Comment:*** **Although this manuscript was well written by the authors, few spelling errors and grammar mistakes were still noted.**

Answer: We appreciate the reviewer for careful reading. We have made every effort to address grammar and spelling issues. Additionally, we also have enlisted the assistance of a native-speaking scholar to revise the manuscript. We sincerely request the reviewer's assistance in identifying any remaining grammar or spelling errors.

To Reviewer 2, Prof. Shyi-Jou Chen:

Thank you for your comments and suggestions. The questions are answered below:

1. ***Comment:*** **Authors mention the cut-point of pre-pandemic seem attribute to global status; however, the outbreak of Taiwan occurred since April 2022. You only divided as pre-pandemic after 2019. Thus, outbreak status should be analyzed.**

   Answer: TPFN now only releases data till the end of 2021. Therefore, we cannot analyze the Taiwan's pandemic in 2022. We have added this issue as a limitation in **Discussion section (Page 12, Line 13 - 16)**.

2. ***Comment:*** **The data are collected from data base, authors did not care these patients, so maternal premature risk factors including perinatal infection or pre-eclampsia etc was not listed as comparison, that is a critical point.**

   Answer: We thank the reviewer for this constructive suggestion. We have presented the number of cases and their proportions for chorioamnionitis and preeclampsia in Table 1, indicating no significant differences between pre-pandemic and during-pandemic groups. Subsequent statistical analyses also have accounted for these factors as covariates, which are listed in the footnote of tables. **(Page 8, Line 12 - 13; Page 9, Line 8)**

3. ***Comment:*** **Perinatal status e.g. APGAR score and RDS score, and respiratory condition is also important, please improve.**

   Answer: We thank the reviewer for the reminder. However, RDS is only a binary variable in TPFN database. The severity of RDS can be surrogated by the usage of surfactant. So, we added the use of surfactant as a covariate in this study. These

data, along with APGAR scores at the first and fifth minutes, are presented in Table 1, showing no differences between pre-pandemic and during-pandemic groups. Subsequent statistical analyses have accounted for these factors as covariates. **(Page 8, Line 9 -10, 16; Page 9, Line 8 - 9)**

4. ***Comment:*** **I also have some critical concerns in table 2,**
   a. **The severity of PVL was not compared, and any cases of multi-pregnancy or birth was not analyzed.**
   b. **The exact gestational age was not list, that is an important confounding factor.**

   Overall, the information or idea is encouraged, but the analysis of your data is not so scientifically or accurately.

   Answer: The data from TPFN did not categorize the severity of PVL. therefore, our analysis is based solely on the presence or absence of PVL. Multi-pregnancy and gestational age have been listed in Table 1 and are adjusted for in those subsequent statistical analyses in Table 3 and 4. Table 2 only compares the raw data of Bayley scale scores. **(Page 8, Line 11 – 12; Page 9, Line 7 – 8; Page 12, Line 16**-17**)**