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Perinatal Morbidity, Mortality, and Neurodevelopmental Outcomes of Neonates with Fetal Growth Restriction

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Abstract

Objective: This study aimed to assess perinatal morbidity, mortality rates, and neurodevelopmental outcomes in the management of fetal growth restriction (FGR) at a single tertiary institute. **Methods:** Among 2465 deliveries between 2013 and 2019, 109 cases of FGR were reviewed retrospectively for causes, indications for pregnancy termination, perinatal death, overall neonatal outcomes, and long-term prognosis. **Results:** Excluding FGR due to congenital anomalies (n = 17), the mortality rate was 3.3% (3/92). One neonate delivered at 23 weeks developed cerebral palsy (1.1%). Retinopathy of prematurity occurred in four neonates (4.3%). Neurodevelopmental disorders were present in six neonates (6.5%), all of whom were delivered at 32 - 38 weeks. Significantly lower gestational age at delivery, lower birth weight, and higher umbilical artery resistance indices were observed in neonates with neurodevelopmental disorders. **Conclusions:** Intact survival before 27 weeks of gestation at delivery with FGR is uncommon. Neurodevelopmental disorders may still develop after delivery at 32 - 38 weeks; consideration should be given to the timing of delivery usingfetal ductus venosus Doppler waveforms measurements to reduce neurodevelopmental disorders.

Keywords

Fetal Death, Fetal Growth Retardation, Neurodevelopmental Disorders, Perinatal Mortality, Umbilical Artery Doppler Velocimetry

1. Introduction

Determining when to deliver a fetus is the only strategy for managing fetal

growth restriction (FGR). FGR is a common condition in pregnancy that is associated with various perinatal outcomes [1]. It is a key cause of perinatal and neonatal mortality as well as suboptimal neurodevelopment [2] [3] [4], with adverse effects in adolescence and adulthood [5].

Due to limited preventive and treatment measures, the management of FGR is based on optimal fetal surveillance and timely delivery, both of which aim to reduce perinatal mortality and morbidity. The goal of perinatal management of FGR is to deliver the neonate at a higher gestational age with fewer neurological sequelae while avoiding fetal death whenever possible. In most cases, the timing of delivery is decided on an individual basis using antenatal fetal surveillance, including cardiotocography (CTG), biophysical profile score (BPS), estimated weight, amniotic fluid volume, and umbilical artery Doppler velocimetry [1].

A previous meta-analysis reported that the odds ratios for the risk of fetal death in fetuses with FGR with absent or reversed umbilical artery velocities prior to 34 weeks of gestation were 3.59 and 7.27, respectively [6]. The Society for Maternal-Fetal Medicine's (SMFM) Consult series recommends delivery at 33 - 34 weeks of gestation for fetuses with FGR and absent end-diastolic velocity (AEDV) in the umbilical artery and at 30 - 32 weeks for fetuses with reversed end-diastolic velocity (REDV) [7]. However, there are no recommendations for fetuses with FGR with AEDV or REDV at <30 weeks [7]. Additionally, there is no clear criterion for delivery in Japan for abnormal umbilical artery Doppler velocity at any point during gestation [8]. Improvements in neonatal care have enabled neonates with severe FGR to be managed, and the impact on child development is now the focus of attention. Since there is no established treatment for FGR, it is important to identify and share the management strategies and prognosis of neonates in each facility. Therefore, this study aimed to identify perinatal morbidity, mortality, and neurodevelopmental outcomes in the management of FGR at a single university hospital.

2. Materials and Methods

In this study, we retrospectively reviewed all cases managed in our department in 2013. The inclusion criteria were all cases of FGR. The exclusion criteria were cases where intrauterine fetal death (IUFD) occurred at the time of the initial visit and cases of fetal congenital anomalies.

In Japan, FGR is defined as an estimated fetal weight of < −1.5 standard deviations (SDs) of the mean weight for gestational age [8]. The current management policy of our department is as follows: when FGR is diagnosed, the mother is hospitalized. CTG is performed twice daily, and abdominal ultrasonography is performed 2 - 3 times per week to assess the following parameters: estimated fetal birth weight (EFW), head circumference, BPS, amniotic fluid volume (amniotic fluid index/amniotic fluid pocket), and Doppler velocity of the umbilical, middle cerebral, and ductal venous arteries. Indications for delivery are made comprehensively based on the following abnormal findings according to Japanese guidelines [8]: CTG abnormalities (moderate or severe variant pattern), abnormal um-

bilical artery Doppler velocity (AEDV/REDV), low BPS (<6), and no significant change in the estimated weight for 2 weeks. FGR is classified as early or late onset based on the gestational age at the time of prenatal ultrasound. Early- and late-onset FGR is diagnosed prior to and after 32 weeks of gestation, respectively [9]. The term "small for gestational age" (SGA) has been used to describe a newborn whose birthweight is less than the 10th percentile for gestational age, and "severe SGA" describes a newborn whose birthweight is less than the 5th percentile for gestational age. Neonates are followed up until 1 year of age and discharged if there are no problems. However, follow-up is continued if developmental abnormalities are suspected. Neurodevelopmental disorders include intellectual disabilities, communication disorders, autism spectrum disorders, attention deficit/hyperactivity, localized learning difficulties, and motor disorders caused by abnormal neurodevelopment in neonates, children, and adolescents.

All procedures were performed according to the ethical standards of the institutional and/or national research committee and in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This retrospective study was approved by the Institutional Review Board of Ryukyu University, Okinawa, Japan (approval no. 1805).

All statistical analyses were performed using JMP software (SAS Institute, Inc., Cary, NC, US). Proportions were compared using Fisher's exact test or chi-square test. Continuous variables were analyzed and compared using the student t-test or Mann-Whitney U test. A p-value of <0.05 was considered statistically significant. Factors independently associated with neurodevelopmental disorders were determined by logistic regression analysis for gestational age at birth, birth weight, and umbilical artery resistance index value.

3. Results

Among the 2465 cases managed in our department from January 2013 to December 2019, 113 (4.6%) had FGR. Three twins and one case of IUFD at the time of initial visit were excluded, and the remaining 109 cases were reviewed for the causes of FGR, indications for delivery, perinatal death, overall neonatal outcomes, and long-term prognosis.

Seventeen cases of fetal congenital anomalies that were included in the analysis of the causes of FGR were excluded from the analyses of other parameters.

3.1. Etiology of Fetal Growth Restriction

Table 1 shows the fetal factors and maternal characteristics of the FGR cases. Overall, 17/109 (15.6%) mothers had fetal factors. Among them, eight (47.1%) had chromosomal abnormalities, five had genetic disorders (29.4%), and four (23.5%) had a fetal diaphragmatic hernia. After excluding those with chromosomal and structural anomalies, 21/92 (22.8%) mothers who had hypertensive disorders of pregnancy (HDP), 4/92 (4.3%) who had gestational diabetes mellitus, and 9/92 (9.8%) who had autoimmune diseases were included. Smoking was noted in 15/92 (16.1%) mothers.

Table 1. Fetal factors and maternal characteristics of FGR cases (n = 109).

Fetal factors	n = 17
Chromosomal abnormality	8 (47%)
Trisomy 18	4
Trisomy 21	2
Trisomy 13	1
Trisomy 9	1
Fetal diaphragmatic hernia	4 (24%)
Genetic disorder	5 (29%)
Ehlers-Danlos syndrome	1
Cornelia de Lange syndrome	1
ARC syndrome	1
Russell-Silver syndrome	1
MICPCH syndrome	1
Maternal characteristics	**n = 92**
Median age (years), range	33 (18 - 41)
Primipara, n (%)	46 (49.4)
BMI (kg/m^2), median (range)	23.5 (15.7 - 34)
Smoking, n (%)	15 (16.1)
Hypertensive disorder of pregnancy, n (%)	21 (22.8)
HELLP syndrome, n (%)	1 (1.1)
Placental abruption, n (%)	1 (1.1)
Gestational diabetes, n (%)	4 (4.3)
Diabetes, n (%)	1 (1.1)
Autoimmune disorders (%)	9 (9.8)
SLE, n (%)	1 (1.1)
Thyroid disorder, n (%)	8 (8.7)
Cytomegalovirus infection, n (%)	1 (1.1)

ARC, arthrography, renal dysfunction, cholestasis syndrome; BMI, body mass index; FGR, fetal growth restriction; HELLP, hemolysis, elevated liver enzymes, low platelet count; MICPCH, microcephaly with pontine and cerebellar hypoplasia syndrome; SLE, systemic lupus erythematosus.

3.2. Perinatal Morbidity and Mortality and Neurodevelopmental Outcomes

The mean gestational age at birth was 36.4 ± 3.7 (23 - 41) weeks, and the mean

birth weight was 2186 ± 591.9 (258 - 2,986) g. Figure 1 shows the neonatal outcomes according to gestational age at delivery. Perinatal death and cerebral palsy (CP) were observed in neonates delivered at <27 weeks and retinopathy of prematurity (ROP) was observed at 28 - 33 weeks. The frequency of ROP was 4.3% (4/92), with one case at 22 weeks, one at 28 weeks, two at 29 weeks, and one at 31 weeks of gestational age at delivery. ROP was not observed in neonates delivered after 32 weeks of gestation, and no significant long-term loss of vision was observed. In contrast, neurodevelopmental disorders were observed in neonates delivered at 32 weeks of gestation.

Table 2 shows the details of perinatal death, CP, and neurodevelopmental disorders. Perinatal death occurred in three cases (2.8%). In Case 1, the EFW at 24 weeks of gestation was 255 g (−3.6 SD); umbilical artery REDV was observed at 23 weeks of gestation, making neonatal resuscitation impossible, and IUFD occurred at 25 weeks of gestation. Case 2 had an EFW of 391 g (−2.7 SD) at 24 weeks of gestation and umbilical artery REDV; although treatment was aggressive, including a caesarean section at 25 weeks of gestation for non-reassuring fetal status, the neonate, who had a birth weight of 440 g, did not survive. Case 3 had FGR detected at approximately 18 weeks of gestation, and placental abruption was observed at 27 weeks; an emergency caesarean section was performed, but the neonate, who was only 700 g, did not survive. Among the four neonates delivered before 27 weeks of gestation, the only survivor (Case 4) was delivered at 23 weeks of gestation; the neonate had an EFW of 405 g (−1.8 SD), and there was no abnormal umbilical artery Doppler velocity (AEDV/REDV). The onset of spontaneous labor was followed by vaginal delivery at 23 weeks of gestation. The neonate developed CP with intraventricular haemorrhage, periventricular leukomalacia, necrotizing enterocolitis, and ROP. Perinatal deaths in cases 1 and 2 were due to low birth weight and prematurity. Case 3 was difficult to resuscitate due to poor fetal condition caused by placenta abruptio. Case 4 presented with cerebral palsy due to prematurity.

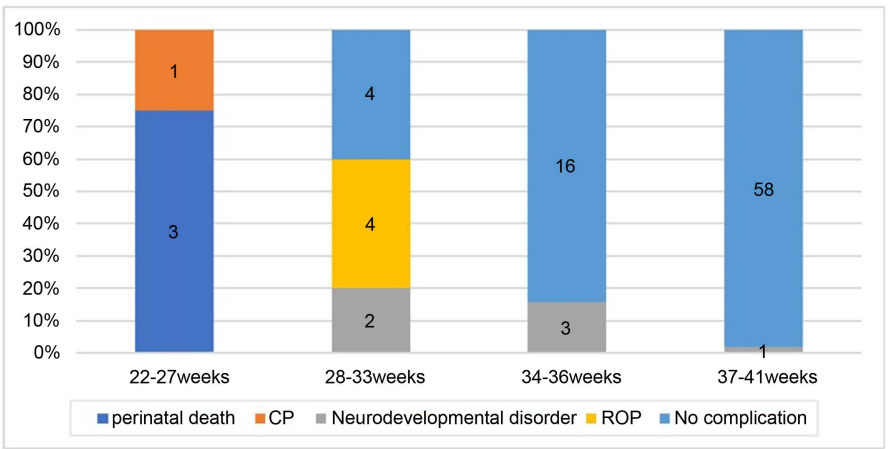

Figure 1. Neonatal complications according to week of delivery. CP, cerebral palsy; ROP, retinopathy of prematurity.

Table 2. Details of perinatal outcomes and neurodevelopmental disorders.

Cases	Gestational Age at Birth (weeks)	Birth Weight (g)	Percentile of Birth Weight	Indication of Delivery	Delivery Methods	Cord pH	AEDV	REDV	Current Status
Perinatal death									
1	25	258	<3rd	IUFD	Vaginal	−	+	+	
2	25	440	<3rd	NRFS	C/S	7.135	+	+	
3	27	700	<3rd	Placenta abruption	C/S	6.8	−	−	
Cerebral palsy									
1	23	436	<10th	Onset of labor	Vaginal	7.19	−	−	
Neurodevelopmental disorders									
1	32	1428	<10th	Onset of labor	Vaginal	7.418	−	−	5 years old, motor developmental disorder
2	33	1436	<10th	Onset of labor	Vaginal	7.38	−	−	6 years old, autism
3	35	1620	<10th	NRFS	C/S	7.295	−	−	6 years old, communication disorders
4	35	1632	<10th	Onset of labor	Vaginal	7.305	−	−	6 years old, autism
5	36	1609	<3rd	NRFS	C/S	7.18	−	−	5 years old, communication disorders
6	38	2306	<10th	Previous C/S	C/S	7.286	−	−	2 years old, communication disorders

IUFD, intrauterine fetal death; AEDV, absent end-diastolic velocity; REDV, reversed end-diastolic velocity; C/S, caesarean section; NRFS, non-reassuring fetal status.

The overall incidence of neurodevelopmental disorders was 6.5% (6/92) (Table 2). Three neonates developed communication disorders, two had autism, and one had a motor developmental disorder. There were four and two neonates with early- and late-onset FGR, respectively, all of whom were delivered after 32 weeks. Six cases with neurodevelopmental disorders were delivered between 32 and 38 weeks and were not expected to have neurodevelopmental disorders at birth. The backgrounds of the cases with and without neurodevelopmental disorders were compared to clarify the risk of neurodevelopmental disorders (Table 3). The results showed lower gestational week and birth weight at birth and higher umbilical artery resistance index values. However, the incidence of early onset and severe SGA did not differ significantly between the two groups.

Table 3. Comparison of maternal and neonatal characteristics between infants with neurodevelopmental disorders and normal development.

	Neurodevelopmental Disorders (n = 6)	Normal Development (n = 86)	p-value
Maternal characteristics			
Age (years)	34 (±3.4)	31.5 (±6.1)	0.14
Primipara (n, %)	3 (50)	42 (51.2)	1
BMI	24.1 (±5.4)	23.4 (±3.8)	0.73
Smoking (n, %)	2 (33.3)	12 (14.6)	0.24
Gestational hypertension (n, %)	2 (33.3)	18 (22.0)	0.61
Gestational diabetes (n, %)	1 (16.7)	2 (2.4)	0.19
Early onset (n, %)	4 (66.7)	53 (61.6)	1
severe SGA (n,%)	1 (16.7)	35 (40.7)	0.39
GA of delivery (weeks)	34.8 (±2.1)	37.2 (±2.8)	0.04
Resistance index value of umbilical artery	0.698 (0.49)	0.62 (0.12)	0.009
Positive AEDV or LEDV (n, %)	0	1 (1.2)	1
Oligohydramnios (n, %)	2 (33.3)	18 (22.0)	0.61
BPS <6 (n, %)	0	4 (4.9)	1
Umbilical artery pH	7.31 (±0.086)	7.30 (±0.07)	0.76
Neonatal characteristics			
Birth weight (g)	1671.8 (±324.1)	2,159.2 (±523.1)	0.012
Birth weight <3rd percentile	3 (50)	34 (41.5)	0.69
Oxygen administration	1 (16.7)	11 (13.4)	1
Intubation	0	1 (1.22)	1

BMI, body mass index; SGA, small for gestational age; GA, gestational age; AEDV, absent end-diastolic velocity; REDV, reversed end-diastolic velocity; BPS, biophysical profile score.

3.3. Indications for Delivery

The indications for delivery are shown in Table 4. Among the 32 mothers who delivered at <36 weeks and 59 mothers who delivered at 37 weeks, there were significantly more deliveries due to CTG abnormalities among those who delivered at <36 weeks than at 37 weeks (37.5% vs. 3%, respectively, $P < 0.01$). Similarly, there were significantly more deliveries due to severe HDP among those who delivered at <36 weeks than at 37 weeks (25% vs. 3.4%, respectively; $P < 0.01$). In contrast, deliveries due to obstetric problems, such as the onset of labor, rupture of membranes, or chorioamnionitis, were significantly more common after 37 weeks. None of the deliveries were due to AEDV or REDV.

Table 4. Indications for delivery according to gestational week.

	Delivery (weeks)		p-value
	22 - 36 (n = 32)	37 - 41 (n = 59)	
CTG abnormalities (n, %)	12 (37.5)	2 (3%)	<0.01
BPS < 6 (n, %)	1 (3.1)	0	–
Oligohydramnios (n, %)	0 (0)	1 (1.7%)	–
HDP (n, %)	8 (25)	2 (3.4)	<0.01
Obstetric indications (n, %)*	9 (28.1)	45 (76.3)	<0.01
Arrest of fetal growth (n, %)	2 (6.3)	9 (15.3)	0.32

CTG, cardiotocography; BPS, biophysical profile score; HDP, hypertensive disorders of pregnancy;*Indications for onset of labor, rupture of membranes, and CAM.

4. Discussion

4.1. Etiology of Fetal Growth Restriction

The etiology of FGR can be divided into maternal, fetal, and placental factors [1]. FGR due to chromosomal abnormalities accounts for 5% - 10% of all cases [7]. In our study, both structural and genetic abnormalities were included, which accounted for 7.3% of the cases. A previous study reported that among 188 FGR cases diagnosed at 22 - 25 weeks of gestation, 28% were due to structural and genetic abnormalities [10]. This rate was higher than that observed in our department because that study only included cases of early-onset FGR. Maternal conditions, including hypertension, antenatal diabetes, renal disease, thyroid disease, autoimmune diseases, and gestational hypertension, may also cause FGR. Furthermore, smoking and alcohol consumption are also associated with FGR. The rate of smoking in our study was 16.1%, which was three times higher than that in the overall population of pregnant Japanese women (5.4%) [11].

4.2. Perinatal Morbidity and Mortality

After excluding FGR due to congenital anomalies, the mortality rate due to FGR was 3.3%, which included one case of IUFD at 25 weeks and one case of delivery at 25 and 27 weeks, respectively. Fetuses diagnosed with an FGR at 18 - 22 weeks with an EFW below the third percentile prior to delivery were considered difficult to save. The presence of an EFW below the 3rd percentile is associated with an increased risk of adverse perinatal outcomes irrespective of the umbilical or middle cerebral artery Doppler indices [12]. Additionally,in a large retrospective cohort of >3 million singleton pregnancies, the risk of stillbirth when the birth weight was below the 3rd percentile was approximately three times higher in the 3rd to 5th percentile group and four to seven times higher in the 5th to 10th percentile group for almost all gestational ages [13]. The risk of IUFD of fetuses with an

EFW below the 3rd percentile was 58.0 per 10,000 fetuses compared with 5.1 for non-small-for-gestational age (SGA) fetuses. Therefore, a threshold of 26 weeks of gestation, weight of 500 g, or both have been proposed for the delivery of severe early-onset FGR pregnancies because of the high incidence of adverse events [14]. The decision to deliver at <26 weeks gestation or at 500 g requires coordination between maternal-fetal medicine and neonatology departments along with comprehensive patient counselling on neonatal morbidity and mortality as well as shared decision-making on pregnancy management [1]. Interestingly, three of the four FGR cases in our study that resulted in perinatal death and CP met these criteria. However, one case who did not meet the criteria but died perinatally and had a birth weight of 700 g, which may have been strongly influenced by placental abruption.

The SMFM recommends delivery at 30 - 32 weeks of gestation for pregnancies with FGR and REDV [7]. If REDV occurs, the mother should be hospitalized, given prenatal corticosteroids, and monitored closely using CTG; delivery should be considered depending on the entire clinical picture and results of additional evaluations of fetal well-being [7]. However, all three cases in our study would have resulted in IUFD if delivery had been delayed until 30 weeks. Therefore, severe early-onset FGR requires new strategies for treatment and prevention in subsequent pregnancies. Women with a previous pregnancy affected by FGR have a 20% - 30% risk of recurrence [15]. Low-dose aspirin in early pregnancy can be effective, whereas low-molecular-weight heparin and sildenafil are not [13]. Previous meta-analyses have demonstrated that prophylactic low-dose aspirin slightly reduced the risk of FGR and SGA [16] [17] [18]. However, these findings were not confirmed in the Aspirin for Evidence-Based Pre-eclampsia Prevention trial, which was primarily aimed at preventing preterm eclampsia [19]. Additionally, the American College of Obstetricians and Gynecologists and the SMFM do not recommend low-dose aspirin for the prevention of FGR due to conflicting evidence [1] [7]. Furthermore, the use of low-molecular-weight heparin does not reduce the risk of recurrent FGR [20] [21]. There is currently no evidence to support the use of therapeutic interventions that enhance blood flow to the uterine placenta through vasodilation for FGR, such as sildenafil [22]. Meanwhile, studies on tadalafil, a phosphodiesterase inhibitor, have been noteworthy. Tadalafil significantly increases daily weight gain, prolongs gestational age, and reduces perinatal and neonate mortality [23]. There were no intact survivors of newborns with FGR delivered at <27 weeks. Effective methods for the prevention and treatment of FGR have not been proven, and further research is required.

4.3. Neurodevelopmental Outcomes

Several studies have demonstrated associations between FGR and delayed cognitive development, behavioral disorders, and academic failure in childhood [1]. In our study, neurodevelopmental disorders had an incidence rate of 6.5%. Signifi-

cantly lower gestational age at delivery, lower birth weight, and a higher umbilical artery resistance index were observed in neonates with FGR and neurodevelopmental disorders compared to those without. Despite a late onset, neonates with intrauterine GR have lower intelligence quotients and more neuropsychological difficulties [24]. In contrast, term neonates with FGR do not have an increased risk of low intelligence scores [25] [26]. A relationship between differences in the corpus callosum (CC) as assessed by fetal magnetic resonance imaging and neurobehavior in intrauterine GR has been reported. The development of the CC was significantly altered in fetuses with late-onset IUGR and correlated with worse neurobehavioral performance. Therefore, the CC may be a potential imaging biomarker for predicting abnormal neurodevelopment in FGR [27].

4.4. Indications for Delivery

The most common indications for delivery in our department were CTG abnormalities in preterm cases and obstetric indications for the induction of labor and rupture of membranes in full-term cases. In 2020, the SMFM recommended delivery at 33 - 34 weeks for early-onset FGR with umbilical artery AEDV (Grade 1B) and REDV (Grade 1B) [7]. On the other hand, the International Society of Ultrasound in Obstetrics and Gynecologyguidelines recommend changes in ductus venosus (DV) Doppler and low short-term variability on computerized phonocardiography as determinants of the timing of delivery [28] [29]. In our study, four fetuses had umbilical artery blood flow abnormalities, but none of the mothers delivered for this indication; the deliveries were instead based on CTG abnormalities. One fetus died in utero at 25 weeks, one was delivered at 25 weeks and developed CP, one was delivered at 29 weeks and developed ROP, and one was delivered at 32 weeks and did not develop any complications. However, fetal DV Doppler waveforms were not measured during the study period. Thus, the six cases with neurodevelopmental disorders had no UV abnormalities, but DV was not measured. In the Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) study on neurodevelopment and intermediate perinatal outcomes, timing of delivery with late changes in DV waveforms may improve developmental outcomes at 2 years of age [30]. Therefore, the DV measurement is currently being applied in the management of FGRs.

4.5. Study Limitations

The limitations of our study include its retrospective design and the small number of cases. Additionally, fetal DV Doppler waveforms and low short-term variability on computerized phonocardiographywere not measured during the study period. The advantage is that the same criteria were used to diagnose and manage the delivery and prognosis of the newborn at each facility.

5. Conclusion

Intact survival before 27 weeks gestation at delivery in FGR is rare. It was ob-

served that neonates with neurodevelopmental disorders had significantly lower gestational age at delivery, lower birth weight, and higher umbilical artery resistance index. Neurodevelopmental disorders may still develop after delivery at 32 - 38 weeks; consideration should be given to the timing of delivery usingfetal ductus venosus Doppler waveforms measurements to reduce neurodevelopmental disorders.

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

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