The Impact of Prenatal Diagnosis and Treatment on Early Neonatal Problems

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ABSTRACT

OBJECTIVE: Obstetric problems have detrimental effects on both pregnancy and newborn. We aimed to examine the relationship between pregnancy complications and newborn morbidities.

STUDY DESIGN: The newborns admitted to the neonatal intensive care unit between September 2019 and August 2022 were included in this retrospective cross-sectional study. Antenatal morbidities and neonatal complications including low APGAR-score (<5), bronchopulmonary dysplasia, early neonatal sepsis, and early neonatal death were evaluated. Pearson-χ^2 cross-tabs were used to compare two variables. A *p*-value <0.05 was determined statistically significant.

RESULTS: Among the 686 infants analyzed, 94 (13.7%) had early neonatal death, 264 (38.5%) had bronchopulmonary dysplasia, 259 (37.8%) had early neonatal sepsis, and 424 (61.9%) had feeding intolerance. Early neonatal sepsis was observed significantly higher in newborns whose mothers had urinary tract infection in the last two weeks (p<0.001), preterm premature rupture of membranes (p=0.006), or clinical chorioamnionitis (p<0.001). Early neonatal death was found significantly higher in pregnancies with preeclampsia (p<0.001), preterm premature rupture of membranes (p<0.001), clinical chorioamnionitis (p<0.001), or small-for-gestational-age (p<0.001). Preeclampsia and magnesium neuroprophylaxis were found significantly higher in neonates with feeding intolerance (p<0.001). Backward: LR logistic regression analysis based on early neonatal sepsis risk revealed that birth week, preterm premature rupture of membranes, clinical chorioamnionitis, small-for-gestational-age, and urinary tract infection were significant parameters affecting the risk of early neonatal sepsis (p<0.05).

CONCLUSION: Preventing premature births and cautious management of pregnancy complications may be helpful in reducing adverse neonatal outcomes. Early detection of high-risk pregnancies and transfer to a tertiary center may be helpful to improve neonatal outcomes.

Keywords: Chorioamnionitis, Early neonatal death, Early neonatal sepsis, High-Risk Pregnancy, Perinatal morbidity, Preterm premature membrane rupture

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Introduction

Adverse prenatal aspects have a crucial impact on the health of the baby both during intrauterine life and during the neonatal period. Neonatal mortality and morbidity are the most consequential effects of prenatal problems. According to the 2018 Turkey Demographic and Health Survey (TNSA) data, 73.5 percent of infant deaths occur during the neonatal period (1). Prematurity is the leading cause of neonatal mortality and morbidity (2). Especially in the last ten years, growth in knowledge and clinical experience, advances in technology, innovations in mechanical ventilation, and antenatal steroid and postnatal surfactant treatments have contributed to a reduction in neonatal mortality and morbidity by increasing the success in the management of respiratory distress syndrome (3,4). On the other hand, the fact that the limit of survival in the external environment was successfully reduced to 500 grams and up to 22 weeks showed the importance of neonatal intensive care services (5).

Obstetric complications such as PPROM and chorioamnionitis are associated with adverse perinatal outcomes. While PPROM affects 3-5% of pregnancies, term deliveries are affected by chorioamnionitis in 90% of cases (6,7). Premature birth, perinatal infections, early neonatal sepsis, septic shock, respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and perinatal mortality are some of these complications (8,9).

Preeclampsia is also a common pregnancy complication, and it is associated with increased premature birth rates and neonatal morbidity risk. In a study that found a 12-fold rise in the risk of premature birth in pregnancies with PPROM, it was shown that this risk increased by 6.6-fold in preeclamptic pregnancies (10). In another study conducted in our country, preeclampsia was reported to occur in 20% of neonatal critical care patients (11).

Comparing the pregnancy complications encountered during the antenatal follow-up to the problems that may arise in the early postnatal period may be important as it may enable the development of life-saving strategies for both the mother and the baby. The purpose of this study was to investigate the relationship of perinatal complications and adverse neonatal outcomes.

Material and Method

This retrospective, cross-sectional study involved premature neonates admitted to the NICU whose mothers applied to the Perinatology Clinic of our hospital and delivered between September 2019 and August 2022. The patients who had accessible medical records were included. Patient data were analyzed retrospectively from hospital information administration system, patient files, and birth records. Clinical and demographic data were recorded. The presence of preeclampsia, PPROM or clinical chorioamnionitis, whether magnesium neuroprophylaxis or an antenatal steroid was administered or not, were recorded from maternal data. Also, gestational week at birth, mode of delivery, birth weight, the presence of a low Apgar (<5), and information such as birth weight <10th percentile for gestational age (SGA, small-for-gestational-age), BPD, feeding intolerance, early neonatal sepsis and early neonatal death were recorded. The relationship between perinatal morbidity and neonatal complications was investigated. Newborns were classified as 24-27 weeks, 28-31 weeks, and 32-34 weeks according to the week of birth. For those who received antenatal steroids, two doses of 12 mg of intramuscular (i.m.) betamethasone were given 24 hours apart during the prenatal period. Patients who received a single dose of an antenatal steroid were not included in the study. Also, patients who had chronic comorbid diseases and were using drugs were excluded. Preeclampsia was defined as new-onset hypertension (blood pressure 140/90 mmHg or higher) after 20 weeks of gestation with proteinuria or the addition of one of thrombocytopenia, renal failure, or elevated liver enzymes (12). Magnesium prophylaxis was used for neuroprotection in <32-week pregnancies and seizure prevention in severe preeclampsia cases. MgSO4 was administered as an intravenous loading dose of 4-6 g (administered slowly over 20-30 minutes), followed by a maintenance dose of 1-2 g per hour for up to 24 hours. Rupture of membranes before <37 weeks was defined as PPROM, and regardless of the duration until birth, all of the patients with rupture of membranes were included in the study. Clinical chorioamnionitis was diagnosed when at least two clinical findings were present, including uterine fundal tenderness, maternal tachycardia (>100/min), fetal tachycardia (>160/min), and purulent or foul-smelling amniotic fluid, in addition to a maternal fever of 38°C or higher. BPD was defined as chronic lung disease requiring O_2 therapy on the postnatal 28th day in infants with severe respiratory distress syndrome who received mechanical ventilation therapy (13). In addition to the clinical findings and elevation in CRP, the diagnosis of sepsis was determined based on the positive blood culture. The study involved cases of early neonatal sepsis that occurred in the first seven days of neonatal life.

Permission was obtained from the Clinical Research Ethics Committee of the hospital before beginning the research (E2-22-2840).

The SPSS 26 (IBM SPSS Statistics 26) program was used for statistical analysis. Descriptive statistics of variables were presented as mean ± standard deviation (SD) or median (range). "Pearson-χ^2" cross-tabs were used to examine the relationships between two qualitative variables. Binary logistic regression: Backward LR model was used to determine the factors affecting adverse neonatal outcomes. *P* value below 0.05 was regarded as statistically significant.

Results

A total of 686 infants were included in the study. The characteristics of the patients were summarized in table 1. The mean gestational age was 28.2±4.7 years, and the mean birth weight was 1071±354.6 grams. 257 (37.5%) of the cases were delivered with cesarean section, and the delivery week of 360 (52.6%) was between 28 and 31 weeks of gestation. 243 (35.5%) of the patients were SGA. The administration rate of magnesium prophylaxis was 42.6% (n=292), and the administration rate of antenatal steroid was 71.5% (n=490) in the study group. While PPROM was found in 29.3% (n=201) of the cases, clinical chorioamnionitis was found in 15.8% (n=108). 458 (66.9%) of the mothers were diagnosed with UTI in the last two weeks and used antibiotics. When neonatal complications were examined; BPD was found in 264 (38.5%), feeding intolerance in 424 (61.9%), ENS in 259 (37.8%), and early neonatal death was determined in 94 (13.7%) of the newborns (Table I).

As presented in table II, the rates of low APGAR (<5), early neonatal death, and ENS increased statistically significantly as the week of birth decreased (p<0.05).

Table I: *Patient characteristics*

Variable	n	%
Gestational week at birth		
24-27 week	205	29.9
28-31 week	360	52.6
32-34 week	120	17.5
Cesarean section	257	37.5
APGAR <5	208	30.4
Preeclampsia	343	50.1
PPROM	201	29.3
Clinic chorioamnionitis	108	15.8
UTI	458	66.9
SGA	243	35.5
Magnesium neuroprophylaxis	292	42.6
Antenatal steroid	490	71.5
Early neonatal death	94	13.7
BPD	264	38.5
ENS	259	37.8
Feeding intolerance	424	61.9

PPROM: Preterm premature ruptures of early membrane rupture, UTI: Urinary tract infection, SGA: Small for gestational age, BPD: Bronchopulmonary dysplasia, ENS: Rarly neonatal sepsis

Table II: *Neonatal complications compared to the week of birth*

Gestational week at birth	24-27 weeks (n=205)		28-31 weeks (n=360)		32-34 weeks (n=120)		*p**
Variable	n	%	n	%	n	%	
Early neonatal death	55	26.8	24	6.7	15	12.5	**<0.001**
BPD	88	42.9	130	36.1	46	38.3	0.277
ENS	105	51.2	114	31.7	40	33.3	**<0.001**
APGAR<5	102	49.8	93	25.8	13	10.8	**<0.001**
Feeding intolerance	138	67.3	213	59.2	73	60.8	0.153

** The relationships between two qualitative variables were evaluated using "Pearson-2" crosstabs.*
BPD: Bronchopulmonary dysplasia, ENS: Early neonatal sepsis

When early neonatal sepsis and prenatal morbidities were compared, early neonatal sepsis was observed to be significantly higher in infants of mothers with UTI (p=0.001), PPROM (p=0.006) and clinical chorioamnionitis (p=0.001) (Table III).

In addition, the rate of early neonatal sepsis was statistically significantly higher in those with preeclampsia (p=0.001), those with SGA (p=0.001), those who received magnesium prophylaxis (p=0.001) or antenatal steroids (p=0.001).

When analyzing the relationship between early neonatal death and prenatal morbidities (Table IV), it was found that the risk of early neonatal death was significantly higher in patients with preeclampsia (p=0.001), PPROM (p=0.001), clinical chorioamnionitis (p=0.001), or SGA (p=0.001).

Evaluating prenatal conditions that may be associated with feeding intolerance (Table V); feeding intolerance was found to be statistically significantly higher in newborns of mothers diagnosed with preeclampsia (p=0.001), those who had a UTI (p=0.001), or those who received magnesium prophylaxis (p=0.001).

As a result of the Backward: LR logistic regression analysis based on the early neonatal sepsis risk and used estimated parameters that may have all the effects in univariate analyses, the optimal model was presented in (Table VI). In the current model, week of birth, PPROM, clinical chorioamnionitis, SGA, and a history of UTI in the previous two weeks were identified as significant risk factors for predicting ENS (p<0.05). When the week of delivery increased by one unit, the risk of ENS decreased 11.1 times. It was determined that the risk of ENS was 2.6 times higher in individuals with PPROM, 8.1 times higher in patients with clinical CA, and 5.4 times higher in patients with UTI. It was observed that those with SGA had a 7-fold increased risk of ENS.

Table III: *The relationship between early neonatal sepsis (ENS) and prenatal morbidities*

Variable	ENS				*p**
	No (n=426)		Yes (n=259)		
	n	%	n	%	
UTI					
No	186	43.7	41	15.8	**<0.001**
Yes	240	56.3	218	84.2	
PPROM					
No	285	66.9	199	76.8	**0.006**
Yes	141	33.1	60	23.2	
Clinic chorioamnionitis					
No	402	94.4	175	67.6	**<0.001**
Yes	24	5.6	84	32.4	
Antenatal steroid					
No	103	24.2	92	35.5	**0.001**
Yes	323	75.8	167	64.5	
Preeclampsia					
No	248	58.2	94	36.3	**<0.001**
Yes	178	41.8	165	63.7	
Magnesium neuroprophylaxis					
No	267	62.7	126	48.6	**<0.001**
Yes	159	37.3	133	51.4	
SGA					
No	331	77.7	111	42.9	**<0.001**
Yes	95	22.3	148	57.1	

** The relationships between two qualitative variables were evaluated using "Pearson-2" crosstabs.*
ENS: Early neonatal sepsis, PPROM: Preterm premature ruptures of membranes, UTI: Urinary tract infection, SGA: Small for gestational age

Table IV: *The relationship between early neonatal mortality and prenatal morbidities*

Variable	Early neonatal mortality				*p**
	No (n=591)		Yes (n=94)		
	n	%	n	%	
Preeclampsia					
No	320	54.1	22	23.4	**<0.001**
Yes	271	45.9	72	76.6	
PPROM					
No	400	67.7	84	89.4	**<0.001**
Yes	191	32.3	10	10.6	
Clinic chorioamnionitis					
No	534	90.4	43	45.7	**<0.001**
Yes	57	9.6	51	54.3	
UTI					
No	188	31.8	39	41.5	0.064
Yes	403	68.2	55	58.5	
SGA					
No	14	70.1	28	29.8	**<0.001**
Yes	177	29.9	66	70.2	
Antenatal steroid					
No	150	25.4	45	47.9	**<0.001**
Yes	441	74.6	49	52.1	
Magnesium neuroprophylaxis					
No	342	57.9	51	54.3	0.511
Yes	249	42.1	43	45.7	

** The relationships between two qualitative variables were evaluated using "Pearson-2" crosstabs.*
PPROM: Preterm premature ruptures of membranes, UTI: Urinary tract infection, SGA: Small for gestational age

Table V: *The relationship between early neonatal mortality and prenatal morbidities*

Variable	Feeding intolerance				*p*
	No (n=261)		Yes (n=424)		
	n	%	n	%	
Preeclampsia					
No	202	77.4	140	33.0	**<0.001**
Yes	59	22.6	284	67.0	
PPROM					
No	174	66.7	310	73.1	0.072
Yes	87	33.3	114	26.9	
Clinic chorioamnionitis					
No	223	85.4	354	83.5	0.496
Yes	38	14.6	70	16.5	
UTI					
No	65	24.9	162	38.2	**<0.001**
Yes	196	75.1	262	61.8	
SGA					
No	161	61.7	281	66.3	0.223
Yes	100	38.3	143	33.7	
Antenatal steroid					
No	92	35.2	103	24.3	0.002
Yes	169	64.8	321	75.7	
Magnesium neuroprophylaxis					
No	124	47.5	269	63.4	**<0.001**
Yes	137	52.5	155	36.6	

** The relationships between two qualitative variables were evaluated using "Pearson-2" crosstabs.*
PPROM: Preterm premature ruptures of membranes, UTI: Urinary tract infection, SGA: Small for gestational age

Table VI: *Logistic regression model based on ENS risk*

				95% Confidence Interval (OR)	
Variable	B	*p*	OR	Low	High
Gestational week	-0.117	0.001	0.889	0.832	0.950
Clinic chorioamnionitis*	2.087	**<0.001**	8.062	3.244	20.035
PPROM*	0.966	**<0.001**	2.627	1.536	4.493
UTI*	1.685	**<0.001**	5.395	3.423	8.502
SGA*	1.940	**<0.001**	6.957	4.107	11.786
Constant	-8.508	0.001	0.001		

PPROM: Preterm premature ruptures of membranes, UTI: Urinary tract infection, SGA: Small for gestational age

Discussion

Premature birth is one of the most significant problems of the perinatal period, and on the rise globally. It is assumed that improvements in perinatal care, increased rate of pregnancies at advanced ages, widespread use of assisted reproductive techniques, and an increase in multiple pregnancies contribute to the rising trend in premature birth rates. Despite the fact that prematurity increases the risk of neonatal mortality and morbidity, survival rates in premature and very low birth weight infants have increased in the last ten years as a result of scientific and technological advances, widespread of postnatal surfactant therapy, innovations in the use of mechanical ventilators, and intensive parenteral and enteral nutrition approaches. But besides all, these newborns face numerous morbidities, including RDS, BPD, NEC, and neonatal sepsis. Neonates born before the 28th week of gestation or weighing less than 1000 grams have a mortality risk of 30-50% and a morbidity risk of approximately 50%. As the week of delivery decreases, the rate of newborn mortality increases. In the study conducted by Batieha et al., which included 21,928 cases, the neonatal mortality rate for births between 20 and 28 weeks was reported to be 10.5%. In addition, they emphasized that 79 percent of all neonatal deaths occur within the first week of life and 42 percent within the first day (14). In our study, the early neonatal mortality rate was 13.7%, with the highest mor-

tality rate occurring before 28 weeks. Gulcan et al. (15) reported neonatal mortality rates as 57% in those between 25-28 weeks, 22% in those between 29-32 weeks, and 27% in those above 32 weeks. In the study of Katar et al. (16), the neonatal mortality rate was found to be 52% in those between 24-28 weeks, 28% in those between 29-32 weeks, and 20% in those above 32 weeks. In this study, we evaluated the early neonatal mortality rate; and found it to be 26.8% in those between 24-27 weeks, 6.7% in those between 28-31 weeks, and 12.5% in those between 32-34 weeks. The mortality rate was significantly higher in neonates born before the 32nd gestational week compared to babies born after the 32nd gestational week. The early neonatal mortality rate was 26.8 percent in premature infants between 24-27 weeks, 6.7 percent between 28-31 weeks, and 12.5 percent between 32-34 weeks. Those born before 32 weeks of gestation had a significantly higher neonatal mortality rate than those born after 32 weeks. Preeclampsia, PPROM, clinical chorioamnionitis, and SGA were significantly more common among the antenatal complications that affect early neonatal death.

The vast majority of premature births occur due to spontaneous preterm labor or PPROM. PPROM is seen in 3-5% of all births and is among the factors that significantly increase the risk of perinatal mortality and neonatal morbidity. Chorioamnionitis is seen in almost half of PPROM cases (6). Intraamniotic infection can result in obstetric complications including placental abruption, postpartum hemorrhage, and placental retention. Neonatal complications such as NEC, intraventricular hemorrhage (IVH), and sepsis, especially RDS, are frequently encountered in proportion to the lower gestational week in premature births. However, in cases of ruptured membranes, infection is a major cause of morbidity and mortality in newborns, as well as prematurity-related complications. Numerous studies (17,18) have reported that histological chorioamnionitis is associated with a higher incidence of culture-proven or clinically suspected neonatal sepsis in premature infants. In a multicenter study, it was shown that clinical chorioamnionitis increased the rates of neonatal sepsis in premature infants but was not related to neonatal mortality (17). In recent publications, the incidence of culture-proven neonatal sepsis in PPROM cases has been reported between 11% and 40% (19,20). In this study, antenatal morbidities including PPROM, clinical chorioamnionitis, UTI, preeclampsia, and SGA were statistically significantly higher in early neonatal sepsis cases. Moreover, we found that the risk of ENS increased 2.6-fold in patients with PPROM and 8.1-fold in patients with clinical chorioamnionitis. ENS is one of the crucial early neonatal complications that can lead to neonatal mortality, and newborns whose pregnancies are complicated by UTI, PPROM, or chorioamnionitis should be closely monitored for perinatal infections.

Low birth weight and prematurity are two of the most significant risk factors associated with the development of BPD. The frequency and severity of BPD have increased, particularly as a result of the survival of infants born before the 26th week of gestation and weighing less than 1000 grams. The reported incidence of BPD increased from 25% at 28 weeks and >2500 g to 85% at 22 weeks and 1000 g (21,22). In our study, 264 (38.5%) of 686 infants had BPD. Eighty-eight (42.9%) newborns diagnosed with BPD were <28 weeks, 130 (36.1%) were between 28-31 weeks, and 46 (38.3%) were >32 weeks and above. In accordance with the most recent data, the majority of newborns diagnosed with BPD were extremely premature. However, there was no statistically significant association between BPD and gestational age or pregnancy complications (p>0.05).

Prenatal magnesium sulfate (MgSO4) prophylaxis in pregnant women between 24-31 weeks of gestation who are at risk of preterm birth has been shown to have a neuroprotective role on the newborn and reduce the risk of cerebral palsy (23). It has been reported that antenatal MgSO4 administration has long-term neuroprotective but short-term negative effects on preterm infants. There are reports that it influences the transition to full enteral feeding and is associated with delayed feeding tolerance (24,25). It has been revealed that the serum magnesium concentration of newborns applied antenatal MgSO4 is higher than normal during the first 72 hours of life, especially in premature infants, and that this situation was linked to feeding intolerance (26). In our study, antenatal magnesium prophylaxis was found to be significantly associated with an increased risk of feeding intolerance. However, the study is limited by the fact that the results of feeding intolerance were not correlated with antenatal magnesium administration, as determined by newborn blood magnesium levels. Numerous studies (27-29) have examined the short- and long-term prognosis of premature infants born to mothers with preeclampsia. While respiratory morbidity is lower in neonates born late preterm (34-37 weeks) to mothers with preeclampsia, RDS is more common in infants born extremely early preterm (<29 weeks) (27). Consensus holds that concomitant growth retardation is associated with increased neonatal mortality rates in pregnancies between 24-32 weeks with severe preeclampsia, and therefore it should be considered an indication for delivery (28).

Preterm birth is common in preeclamptic patients, with a reported rate of approximately 70%, with 15% occurring before the gestational age of 28 weeks (29). In a study evaluating newborns born between 24 and 36 weeks, it was shown that being born from a preeclamptic mother alone increased the risk of RDS by 1.35 times, and this increase was 1.93 times if the newborn was under 32 weeks (30). The increase in morbidity and mortality in very low-birth-weight infants born to preeclamptic mothers appears to be due to prematurity problems rather than preeclampsia. Although no direct relation to neonatal sepsis has been found, it has been demonstrated that neutropenia is common in infants of preeclamptic mothers and that neonatal inflammation markers are higher in those lower

than 32 weeks (31). In conclusion, newborns born to preeclamptic mothers have an increased risk of early neonatal and long-term neurodevelopmental disorders. We observed that the presence of maternal preeclampsia was significantly higher in newborns with early neonatal sepsis or early neonatal death. However, there is a need for large-scale prospective studies in which patients are grouped according to the severity of preeclampsia and serum inflammation parameters are evaluated for the correlation of neonatal and maternal outcomes.

Small-for-gestational-age, which is defined as a birth weight below the 10th percentile based on the gestational week, occurs in approximately 3-7% of all pregnancies, and this rate rises to 20-25% in the data of large reference hospitals and perinatal centers that follow high-risk pregnant women (32-34). Perinatal mortality increased in proportion to the severity of growth retardation in both term and preterm SGA infants and was 12 to 20 times higher than in SGA infants born at term (35,36). Independent of the week of birth, increased ICU admission, hypoglycemia, polycythemia, and severity of prematurity are associated with substantially increased respiratory distress, bronchopulmonary dysplasia, intraventricular hemorrhage, feeding intolerance, necrotizing enterocolitis, sepsis, convulsions, periventricular leukomalacia, and prematurity (32-36). Long-term complications include neurodevelopmental disorders such as growth retardation and cognitive dysfunction, low social intelligence, attention deficits, and intellectual disabilities (37). In our study, 35.5% of the 686 infants followed in the NICU were SGA, and early neonatal death and ENS were significantly higher in SGA infants, consistent with the literature. Based on the regression analysis, the risk of ENS increased sevenfold in SGA infants. Due to impaired cellular immunity, it is known that SGA newborns have an increased risk of early and late neonatal sepsis. Thomas et al. (38) reported that the total T-cell, helper T-cell, and B-cell counts in SGA neonates were significantly lower than in gestational age-matched infants. In addition, impaired Natural Killer (NK) cell functions, which play a crucial role in defense against viral agents, and smaller thymus sizes in comparison to normally developing fetuses may be associated with an increased risk of infection in SGA neonates (39). In addition, it has been demonstrated that SGA neonates have low T and B cell counts at birth, with the T lymphocyte count rising to normal during childhood despite a low proliferative capacity (40). In conclusion, SGA is a substantial pregnancy complication that causes perinatal mortality and morbidity during both the neonatal and childhood periods, and it should be monitored closely. Detailed studies that analyze neonatal complications by categorizing patients based on percentile curves may be beneficial.

Conclusion

This study includes a large number of extremely premature cases since it covers the perinatology center which most of the high-risk pregnancies in the area are referred. Various morbidities have been noted in extremely premature infants, whose survival rate has been increasing. If antenatal complications can be reduced, neonatal morbidity can also be reduced. To reduce adverse neonatal outcomes, high-risk pregnancies should be detected at an early stage via careful antenatal follow-up; premature births should be prevented as much as possible through cautious monitoring and management; and in cases which cannot be prevented, these high-risk infants should be handled carefully in terms of possible neonatal morbidities.

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Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request. The datasets and code used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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