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Identification of risk factors for necrotizing enterocolitis in twins: a case-control matching analysis of over ten-years' experience

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Abstract

Objective The identification of risk factors is crucial for the clinical prevention and diagnosis of necrotizing enterocolitis (NEC). Monochorionic twins (MCT), due to the high genetic homogeneity, provided a valuable model for investigating the risk factors of various diseases. This study aimed to explore the risk factors for NEC using MCT.

Methods A retrospective review was conducted on the medical records of monochorionic twins (MCT) treated at Guangzhou Women and Children's Medical Center from January 2012 to March 2023. We compared perinatal condition, feeding and preceding condition between MCT pairs with NEC (NEC MCT) and without NEC(No NEC MCT). Logistic regression analysis was utilized to identify independent risk factors.

Result In 85 pairs of monochorionic twins (MCT), NEC occurred in one twin in 78.8% of cases, whereas both twins were affected in 21.2% of cases. In the final cohort of 60 pairs of MCT, several parameters were found to differ significantly between NEC MCT group and No NEC MCT group. Compared to No NEC MCT group, the incidence of umbilical cord abnormalities was significantly higher in the NEC MCT group (25% vs. 8.3%, $P=0.014$). Meanwhile, NEC MCT group showed higher prevalence of SGA infants (48.3% vs. 21.7%, $P=0.002$) and sFGR (38.3% vs. 6.7%, $P=0.000$). Furthermore, TTTs (13.3% vs. 3.3%, $P=0.027$) and septicemia (25% vs. 5%, $P=0.002$) were more common in NEC MCT group. In a multivariable logistic regression model, sFGR (OR 6.81,95%CI 2.1–21.9, $p=0.001$) was eventually output as an independent risk factor.

Conclusion Non-genetic factors play a predominant role in the pathogenesis of NEC. Umbilical cord abnormalities, SGA, sFGR, TTTs and septicemia significantly increase the risk of NEC. sFGR is an independent risk factor of NEC.

Keywords Necrotizing enterocolitis, Monochorionic, Twins, Risk factor

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Introduction

Necrotizing enterocolitis (NEC) is a leading cause of neonatal death, especially among premature infants [1, 2] Despite enhanced pathophysiological understanding and advancements in neonatal intensive care, the overall mortality ratio for this condition maintains high, ranging from 25–40% [3, 4]. Worsening, long-term complications, such as neurodevelopmental deficits, short bowel syndromeand pulmonary pathologies, dramatically impair quality life of the survivor [5–7]. Identifying risk factors is crucial for developing early prevention and treatment strategies for NEC. Nonetheless, there exists a divergence of opinions among clinicians and experts regarding the relative significance of different risk factors. Monochorionic twins (MCT) develop from a single fertilized egg and share the same intrauterine environment [8]. Moreover, the highly homogeneous genetic background of MCT makes them a valuable cohort for investigating the influence of genetic and environmental factors on disease pathogenesis. HACK, et al. [9] reported an incidence rate of 3.8% for NEC MCT in twins hospitalized in the neonatal intensive care unit (NICU). Among MCT twins, those with NEC and without NEC represent a unique aspect to explore the etiological aspects of this condition. However, there is limited research on MCT associated with NEC. This study aimed to explore the risk factors of NEC using MCT.

Patients and methods

This case-control matching study was conducted at Guangzhou Women and Children's Medical Center, the largest tertiary medical center in southern China. The twin pairs would be included: (1) one or both of them developed NEC(≥Bell's stage II); (2) born and treated at our center from January 2012 to March 2023. NEC(≥Bell's stage II) was diagnosed by Bell's criteria according to clinical manifestations(bloody stool, etc.) and imaging findings (pneumatosis intestinalis, portal venous gas, pneumoperitoneum, etc.) [4, 10]. The NEC twin pairs would be excluded: (1) Identified as Dichorionic twins with NEC; (2) Chorionic nature could not be determined; (3) Both twins develop NEC; (4) Combined with congenital intestinal anomalies; (5) Death before NEC; (6) Missing medical records. The study was approved by Medical Ethics Committee of Guangzhou Women and Children's Medical Center and strictly observed the declaration of Helsinki.

Regarding feeding, our center maintains a consistent neonatal feeding strategy. Newborns are primarily fed breast milk, either directly from the mother or from a donor. If breast milk is insufficient and donor milk is refused, preterm infants are given preterm formula. Based on birth weight, initial milk volumes vary. Neonates with smaller birth weights receive less milk and take longer to reach full enteral feeding. (1) Minimal Enteral Nutrition (MEN): At the start of enteral feeding, a small amount of breast milk or formula (usually 0.5-1 ml/kg/h) is given to stimulate gut maturation and peristalsis [11]. (2) Incrementally increase feeding volumes: Adjust daily based on the preterm infant's tolerance, typically increasing by 10–20 ml/kg each time. Monitor the infant's gastrointestinal function closely, including gastric residuals, vomiting, abdominal distension and stool characteristics [12]. When the feeding volume reaches 60 ml/kg/day, half-strength fortified breast milk or preterm formula (81 kcal/100 ml) can be used. When the feeding volume reaches 100 ml/kg/day, full-strength fortified breast milk can be introduced [13–15]. The main nutritional management objectives are as follows [16]: (1) Full enteral feeding volume: 150–180 ml/kg/day; (2) Caloric intake target: approximately 120 kcal/kg/day.

Data collection

We gathered perinatal characteristics, including maternal, obstetrical, and neonatal factors: unequally shared placenta, umbilical cord abnormalities, small for gestational age (SGA), selective fetal growth restriction(sFGR), TTTs, delivery room resuscitation, gestational age at birth, Apgar scores, birth weight and sex. Additionally, we collected the characteristics of feeding strategies, including day of the first feed, type of nutrition (breast milk, formula, breast milk fortified or fasting), the volume of the first feed, and feeding intolerance (FI) before the onset of NEC. Furthermore, we documented preceding condition of NEC: neonatal respiratory distress syndrome (NRDS), severe anemia, septicemia, congenital heart disease (CHD), pulmonary hypertension, intermittent hypoxemia.

Definition

(1) Small for gestational age (SGA) was operationally defined as birth weight below the 10th percentile for the corresponding gestational age [17–19]; (2) Septicemia was defined as systemic signs of infection, deterioration of clinical condition with the presence of positive blood or cerebrospinal fluid cultures in laboratory tests [20–22]. Only Septicemia was detected before the diagnosis of NEC was included in this study; (3) Umbilical cord abnormalities were defined as any deviations from the normal structure, function, or position of the umbilical cord during pregnancy and diagnosed based on findings from ultrasound examinations [23–25]. The umbilical cord can be divided into [25]: 1) Abnormal length; 2) Cord insertions site abnormalities; 3) Cystic abnormalities; 4) Cord hematomas; 5) Solid or complex malformations; 6) Knots; 7) Nuchal cord; 8) Vascular anomalies; 9) Funic presentation and prolapse cord; (4) Selective fetal growth restriction(sFGR) in MCT needs to meet at

least two of the following standards: 1) EFW < 10th percentile for one twin; 2) AC < 10th percentile for one twin; 3) EFW discordance between twins ≥ 25%; 4) Umbilical artery pulsatility index of the smaller twin > 95th percentile [26–29]; (5) Twin-to-Twin Transfusion Syndrome (TTTs) was characterized by the presence of blood flow via arteriovenous anastomoses in both directions, serving as a prerequisite for the development of TTTs. In this syndrome, one fetus acts as the donor, while the other assumes the role of the recipient in the event of an imbalance [30–32]. Ultrasound finding appear severe amniotic fluid discordance between the twins' amniotic sacs. The recipient fetus shows increasing polyhydramnios due to fetal polyuria defined as the deepest vertical pocket of ≥ 8 cm depth before 20 weeks and ≥ 10 cm after 20 weeks of gestation. The donor shows oligo- or anhydramnios with the deepest vertical pocket ≤ 2 cm and is stuck within its membranes to the uterine wall or placenta by the excessive polyhydramnios of the recipient [33]; (6) Feeding intolerance (FI) manifested as gastrointestinal symptoms [34, 35], including a notably large gastric residual volume (> 50% of the previous feeding), vomiting, abdominal distension, bloody stool, visible bowel loops and diarrhea; (7) Unequally shared placenta was defined as one of twin receiving less than 60% of the blood from the placenta, according to the respective area of placental surfaces measured postnatally [23]; (8) Neonatal respiratory distress syndrome (NRDS) was defined as a condition of pulmonary insufficiency that in its natural course commences at or shortly after birth and increases in severity over the first 2 days of life. The diagnostic indicator included [36]: 1) chest X-ray with a classical "ground glass" appearance and air bronchograms; 2) PaO_2 < 50 mmHg (< 6.6 kPa) in room air; 3) central cyanosis in room air or need for supplemental oxygen to maintain PaO2 > 50 mmHg (> 6.6 kPa) as well as classical chest X-ray appearances; (9) Intermittent hypoxemia was defined as a condition where blood oxygen saturation periodically dropped below 85–90% and subsequently returned to normal levels [37]; (10) Severe anemia was defined as hemoglobin less than 60 g/L [38]; (11) Pulmonary hypertension was diagnosed [39]: 1) partial pressure of oxygen in arterial blood (PaO2) < 55 mmHg despite fraction of inspired oxygen (FiO2) of 1.0; 2) a preductal to postductal oxygen gradient greater than 20 mmHg; 3) extrapulmonary right-to-left shunting at the ductal or atrial level in the absence of severe pulmonary parenchymal disease and tricuspid regurgitation; 4) pulmonary arterial pressure (PAP) greater than 25 to 30 mmHg in cardiac catheterization; (12) Congenital heart disease (CHD) was defined as a range of structural abnormalities of the heart and the large blood vessels present from birth. In our study, the isolated patent ductus arteriosus and patent foramen ovale were not included in the scope of congenital heart disease [40, 41].

Statistical analysis

Statistical analyses were conducted using SPSS 25.0 Statistics for Windows software. Comparisons for quantitative variables were made using Student's t-test or the Wilcoxon test, depending on which was appropriate after checking for normality using the Kolmogorov-Smirnoy test. Continuous variables following a normal distribution were presented as mean ± SD. For continuous variables that did not adhere to a normal distribution, data were expressed as quartiles (M, Q1, Q3). Associations between qualitative variables were analyzed using Pearson's chi-squared test. Variables found to have a p value < 0.05 in the univariate analysis would be put into the stepwise logistic regression. The output value with a significance level of $p < 0.05$ was independent risk factors eventually.

Results

From January 2012 to March 2023, our hospital recorded a total of 114,642 cases of newborns. Among these, there were 16,374(14.28%) cases of twin births, 5826(5.08%) cases of monochorionic twin births, and 1547(1.37%) cases of NEC.

A total of 189 twin pairs with NEC were born and subsequently admitted to the study institution between January 2012 and March 2023. Among these, 92 twin pairs were diagnosed with dichorionic twins with necrotizing enterocolitis (DCT-NEC). Due to the lack of records, the 12 pairs of twins could not be confirmed as monochorionic or dichorionic twins and were therefore excluded. Of the 85 pairs of monochorionic twins, 18 pairs all had NEC, 3 pairs had congenital intestinal malformations, and 4 pairs had intrauterine death, which were excluded. Eventually, 60 MCT pairs were included in the study (Fig. 1). In 85 pairs of MCT with NEC(Fig. 2), the GA at birth for infants ranged from 26^{+6} to 37^{+2} weeks. The detailed distribution of GA included the following categories: term infants (6, 3.5%), late preterm infants (62, 36.5%), moderate preterm infants (30, 17.6%), very preterm infants (46, 27%), and extremely preterm infants (26, 15.3%). Regarding birth weights among the NEC MCT cases, the distribution was as follows: normal birth weight infants (16, 9.4%), low birth weight infants (90, 52.9%), very low birth weight infants (36, 21.2%), and extremely low birth weight infants (28, 16.5%).

In the NEC MCT group, the diagnosis time was 13(5.0–22.0) days. The perinatal and delivery characteristics of the two groups are summarized in Table 1. No statistically significant differences were observed between the groups in terms of birth order, birth weight, Apgar scores, the presence of Unequally shared placenta, or the

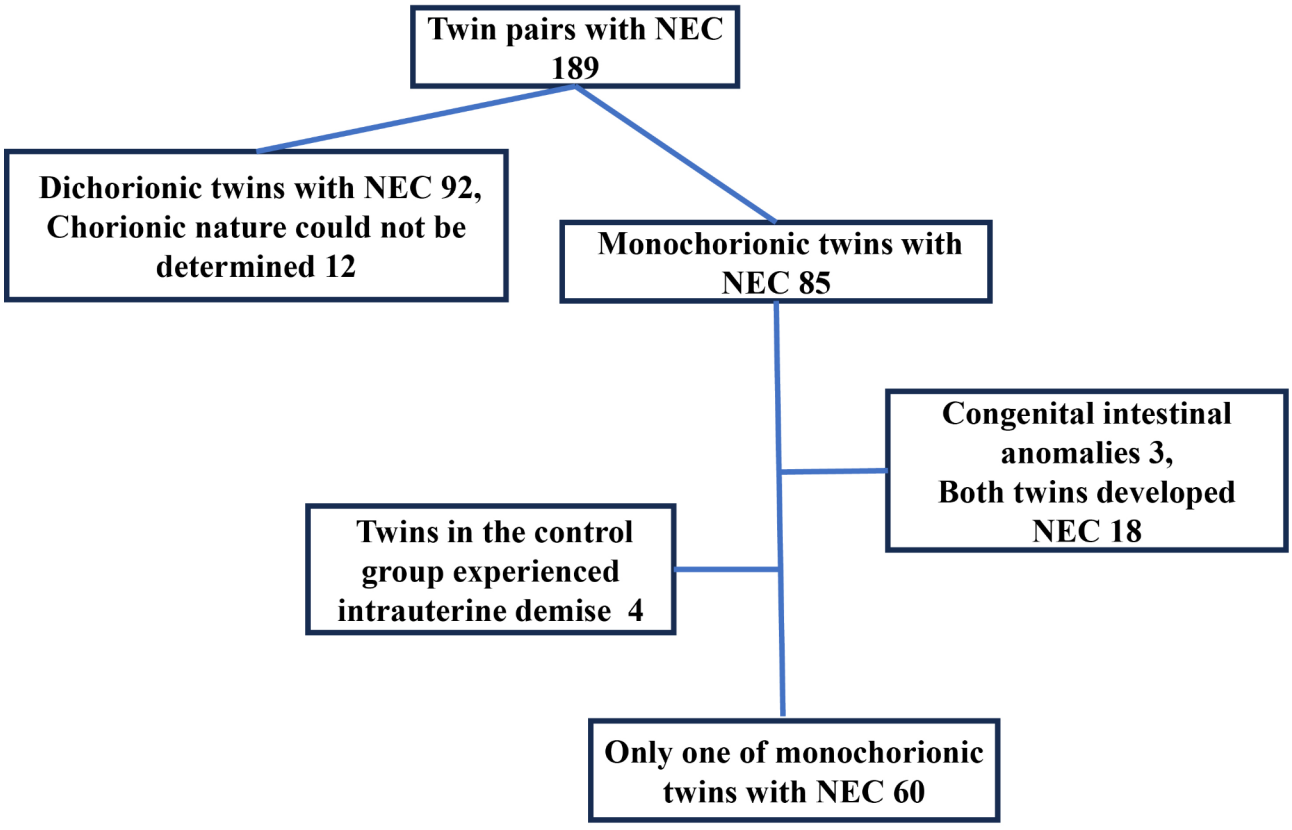

Fig. 1 Flowchart in selection of twin pairs with NEC

need for delivery room resuscitation. NEC MCT cases exhibited a higher incidence of umbilical cord abnormalities (25% vs. 8.3%, $p=0.014$), a greater proportion of SGA infants (48.3% vs. 21.7%, $p=0.002$), a higher prevalence of sFGR (38.3% vs. 6.7%, $p=0.000$), and a higher prevalence of blood donor (13.3% vs. 3.3%, $p=0.027$).

The feeding condition between NEC MCT group and No NEC MCT group is summarized in Table 2. In 120 cases of MCT newborns, no neonates were fed raw cow's milk. 4 cases received donor milk due to insufficient breast milk supply, and 1 case developed necrotizing enterocolitis (NEC). 13 cases received fortified breast milk and 5 cases developed NEC. Among the MCT, 2 MCT pairs received fortified breast milk, and one of MCT pairs developed NEC. In the NEC MCT group, the feeding volume at the onset of NEC increased to 113.9±68.2 ml/kg/day, whereas in the No NEC MCT group, it was 104.6±62.7 ml/kg/day. The time to reach full enteral feeding was 10(8.0–17.0) days in the NEC MCT group, compared to 11(8.0–20.0) days in the No NEC MCT group. During the process of increasing feeding volume, 26 cases exhibited feeding intolerance. Among these, 16 cases were observed in the NEC MCT group.

The incidence of preceding condition was shown in the Table 3. It is notable that the number of infants diagnosed with septicemia was significantly higher in the NEC MCT group (25% vs5%, $p=0.002$). Severe anemia, congenital heart disease (CHD), pulmonary hypertension, and intermittent hypoxemia, showed no discernible differences between the NEC group and the control group.

In the logistic regression analysis, sFGR (OR 6.8,95%CI 2.117–21.911, $p=0.001$) was eventually output as a significant independent risk factor for NEC (Table 4).

Discussion

While clinical features and risk factors of NEC have been extensively documented in the literature, there is a paucity of studies specifically addressing twin NEC [42–44], with most existing reports being limited to case studies involving MCT and often associated with TTTs [42, 43]. To the best of our knowledge, this is the first and largest study on NEC MCT in the South China region, which will help us to more accurately and deeply identify the incidence and risk factors for NEC. In our study, a total of 85 cases of NEC MCT were examined. Among them, 18 cases (21.2%) exhibited simultaneous development of NEC in both monochorionic twins, while 67 cases (78.8%) involved only one twin being affected. These findings suggest that non-genetic factors play a more prominent role in the pathogenesis of NEC in MCT compared to genetic factors. Recently, Rebai et al. [45] reviewed and

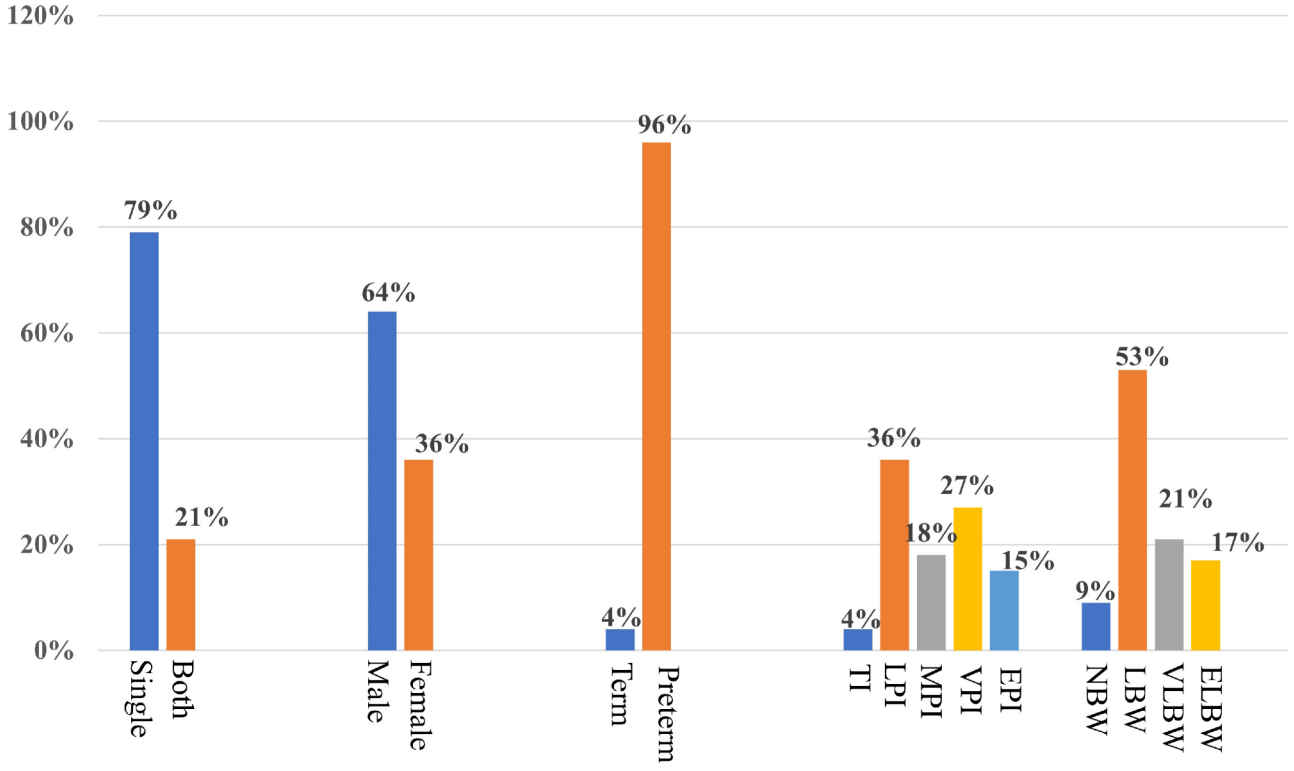

Fig. 2 Demographic information of MCT with NEC. Single: NEC occurred in one case of MCT; Both: NEC occurred in both cases of MCT; TI: term infants; LPI: late preterm infants; MPI: moderate preterm infants; VPI: very preterm infants; EPI: extremely preterm infants; NBW: normal birth weight infants; LBW: low birth weight infants; VLBW: very low birth weight infants; ELBW: extremely low birth weight infants

Table 1 Comparison of perinatal condition between NEC MCT group and no NEC MCT group

	NEC MCT G'roup ($n=60$)	No NEC MCT group ($n=60$)	*P*-value
Smaller twin, n (%)	32(53.3%)	28(46.7%)	0.465
Birth weight, n (%)			0.51
ELBW	9(15%)	6(10%)	
VLBW	12(20%)	8(13.3%)	
LBW	34(56.7%)	38(63.3%)	
NBW	5(8.3%)	8(13.3%)	
BW, g	1743.2 ± 568.7	1884.1 ± 468.1	0.184
Apgar scores [IQR]			
1-minute	9(8.0 ~ 9.0)	9(8.0 ~ 9.0)	0.648
5-minute	9(9.0 ~ 9.0)	9(9.0 ~ 10.0)	0.292
10-minute	9(9.0 ~ 9.0)	9(9.0 ~ 10.0)	0.328
Unequally shared placenta	4(6.7%)	3(5%)	0.697
Umbilical cord Abnormalities, n(%)	15(25%)	5(8.3%)	0.014
SGA, n (%)	29(48.3%)	13(21.7%)	0.002
sFGR, n (%)	23(38.3%)	4(6.7%)	0.000
TTTs, n (%)			0.027
Blood donor	8(13.3%)	2(3.3%)	
Blood recipient	2(3.3%)	8(13.3%)	
Delivery room Resuscitation, n (%)	20(33.3%)	16(26.7%)	0.426

LBW: extremely low birth weight; VLBW: very low birth weight; LBW: low birth weight; NBW: normal birth weight; BW: birth weight; SGA: small-for-gestational-age; sFGR: selective fetal growth restriction; TTTs: twin transfusion syndrome

Table 2 Comparison of feeding condition between NEC MCT group and no NEC MCT group

	NEC MCT group($n=60$)	No NEC MCT group($n=60$)	*P*-value
Day of first feeds/d	1(1.0 ~ 1.0)	1(1.0 ~ 1.0)	0.763
Volume of first fed/ml/kg.d	18(13.4 ~ 21.1)	16.1(12.4 ~ 20.0)	0.540
Day of full feeding/d	10(8.0 ~ 17.0)	11(8.0 ~ 20.0)	0.340
Feeding increment ml/kg/d	113.9 ± 68.2	104.6 ± 62.7	0.526
Feeding, n (%)			0.622
Breastfeeding	12(20%)	15(25%)	
Preterm formula	(38.3%)	20(33.3%)	
Regular formula	1(1.7%)	1(1.7%)	
Combination	22(36.7%)	24(40%)	
Fasted	2(3.3%)	0(0)	
Breast milk fortified	5(8.3%)	8(13.3%)	0.378
FI	16(26.7%)	10(16.7%)	0.184

FI: feeding intolerance

Table 3 Comparison of preceding condition between NEC MCT group and no NEC MCT group

	NEC MCT group($n=60$)	No NEC MCT group($n=60$)	*P*-value
NRDS, n (%)	28(46.7%)	23(38.3%)	0.356
Severe anemia, n (%)	13(21.7%)	12(20%)	0.822
Septicemia, n (%)	15(25%)	3(5%)	0.002
CHD, n (%)	8(13.3%)	3(5%)	0.114
Pulmonary hypertension, n (%)	4(6.7%)	4(6.7%)	1.000
Intermittent hypoxemia, n (%)	8(13.3%)	11(18.3%)	0.453

NRDS: neonatal respiratory distress syndrome; CHD: congenital heart disease

Table 4 Variable output from logistic regression analysis

Variable	OR (95% CI of OR)	*P*-value
sFGR	6.81(2.1–21.9)	0.001

sFGR: selective fetal growth restriction

analyzed 17 cases of NEC MCT and 17 cases of No NEC MCT in a single center. It's found that in the NEC MCT group, birth weight was significantly lower. However, TTTs and SGA did not show significant differences when comparing the NEC MCT group with the no NEC MCT group which may be influenced by the limited number of patients. Through the analysis of 60 cases of NEC MCT and 60 cases of No NEC MCT, we found that umbilical cord abnormalities, SGA, sFGR, TTTs, and septicemia were risk factors for NEC MCT. sFGR can be considered an independent risk factor of NEC.

As neonatal intensive care medicine and perinatal care have advanced, the survival rates of SGA infants have improved progressively. Our analysis revealed a significantly higher proportion of SGA infants in the MCT NEC group compared to the control group (48.3% vs. 21.7%, $p<0.05$), underscoring the association between SGA status and the occurrence of NEC in MCT. A cohort study conducted by Ree et al. [46], which included 475 SGA neonates, reported that the incidence of NEC in SGA infants was 2.6 times higher than that in appropriately sized infants for their GA. Similarly, a study by Boghossian et al. [47]. also found that SGA increased the risk of NEC and with the gestational age increasing, the risk of NEC may increases further.

The umbilical cord, encompassing two umbilical arteries and a vein, serves as the sole conduit providing vital life support to fetuses. Normal development umbilical cord can enhance resistance to torsion, stretching and compression while allowing for unimpeded fetal movements. The two umbilical arteries and their associated anastomoses play a crucial role in ensuring the equitable distribution of blood to the various lobes of the placenta [48]. However, when these favorable mechanisms within the umbilical cord are compromised, the developing fetus becomes vulnerable to various risks. Consequently, umbilical cord abnormalities are associated not only with intrapartum fetal heart rate (FHR) irregularities, low Apgar scores, and neonatal mortality but also with fetal growth restriction, preterm labor, and fetal demise [49]. It is notable that umbilical cord abnormalities are frequently overlooked as risk factors for the development of NEC [50, 51]. Kamoji et al. [52]. found that antenatal umbilical cord abnormalities, leading to inadequate blood perfusion, were high-risk factors for the development of NEC. In our study, we identified 15 cases (25%)

of NEC MCT characterized by umbilical cord developmental abnormalities during the fetal period. Among these cases, 10 exhibited abnormalities in cord attachment, including one instance with a single umbilical artery (SUA), while 5 cases presented with a thin umbilical cord.

sFGR and TTTs are complex and severe complications that specifically affect monochorionic twins (MCT), with estimated incidence rates of 8–15% in such pregnancies [8, 53]. A cohort study by Weisz et al. revealed that among MCT neonates, those with type III sFGR exhibited a significantly higher risk of developing NEC compared to those without sFGR [54]. Furthermore, our study findings underscored distinct distributions in the proportions of TTTs donors and recipients among MCT neonates with or without NEC ($p<0.05$), suggesting a potential association between TTTs and the development of NEC. The underlying mechanisms may involve blood donors experiencing insufficient circulation, leading to compromised gastrointestinal and renal perfusion. This, in turn, triggers activation of the renin-angiotensin-aldosterone system (RAAS), resulting in peripheral vasoconstriction and exacerbating intestinal ischemia and hypoxia. Concurrently, the blood-receiving fetus may suffer from congestive heart failure due to circulatory overload, leading to gastrointestinal stasis. This condition impairs oxygen exchange and toxin metabolism, potentially serving as a causative factor for the development of intestinal lesions in the affected fetus [32, 55].

Gagliardi et al. [56] conducted a multi-center study involving 2035 samples, where they identified late-onset sepsis as an independent risk factor for the development of NEC in very low birth weight (VLBW) infants. Their findings revealed that late-onset sepsis occurred at a rate 5.4 times higher in the NEC population than in the non-NEC population (odds ratio [OR] = 5.38, $p<0.001$). Likewise, Lambert et al. reported a similar association between early-onset sepsis and NEC in term and near-term infants (GA > 36 weeks) [57]. In our study of 15 cases of MCT diagnosed with sepsis before the development of NEC, we observed that this cohort included 10 cases of late-onset sepsis and 5 cases of early-onset sepsis. This distribution differed significantly when compared to non-NEC newborns ($p=0.002$).

The main limitations of this study are its retrospective design and the limited number of patients. However, compared to previous studies, we included a sufficient number of MCT to explore the risk factors for NEC. Additionally, we conducted a comprehensive analysis of NEC MCT, considering perinatal condition, feeding practice and preceding condition. These explorations provided significant indicators and conclusions, underscoring the importance of non-genetic factors such as fetal growth and infection in the occurrence of NEC. Large-sample and multicenter trials are needed to further investigate the risk factors for NEC by MCT.

Conclusions

Non-genetic factors play a predominant role in the pathogenesis of NEC. Umbilical cord abnormalities, small for gestational age, selective fetal growth restriction, twin transfusion syndrome, and septicemia significantly increased the risk of NEC. sFGR is an independent risk factor of NEC. The identification of these risk factors in MCT will contribute to reinforce perinatal management strategies and aid in the prevention of NEC progression.

Abbreviations

NEC	Necrotizing enterocolitis
MCT	Monochorionic twins
DCT	Dichorionic twins
AGA	Appropriate for gestational age
SGA	Small-for-gestational-age
sFGR	Selective fetal growth restriction
TTTs	Twin transfusion syndrome
SUA	Single umbilical artery
FI	Feeding intolerance
NRDS	Neonatal respiratory distress syndrome
CHD	Congenital Heart Disease
TI	Term infant(GA ≥ 37 W)
LPI	Late preterm infant(34 ≤ GA < 37 W)
MPI	Moderate preterm infant(32 ≤ GA < 34 W)
VPI	Very preterm infant(28 ≤ GA < 32 W)
EPI	Extremely preterm infant (GA < 28 W)
NBW	Normal birth weight (BW ≥ 2500 g)
LBW	Low birth weight (1500 g ≤ BW < 2500 g)
VLBW	Very low birth weight (1000 g ≤ BW < 1500 g)
ELBW	Extremely low birth weight (BW < 1000 g)

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Author contributions

Qiuming He and Wei Zhong conceptualized and designed this study. Pengjian Zou, Lili Wu and Wenhai Fang jointly collected the original data of the study subjects. Pengjian Zou, Qiuming He and Huimin Xia set up the research method of the article. Wenhai Fang and Pengjian Zou drafted the initial version of this paper, Wenhai Fang and Lili Wu carried out the initial analyses. Juan He, Wei Zhong coordinated and supervised data collection. Huimin Xia and Qiuming He conducted formal analysis, critically reviewed the writing and edited of this paper.

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Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to privacy or ethical restrictions but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The research ethics committee of Guangzhou Women and Children's Medical Center approved the study. Considering the retrospective nature of this study, ethics committee of Guangzhou Women and Children's Medical Center approved the waiver of parents' written consent. The waiver will not adversely affect the rights and welfare of the patients.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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