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Original Article

Risk factors for brain injury in premature infants with twin-to-twin transfusion syndrome: a retrospective cohort study

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Background: Brain injury (BI) is prevalent in premature infants with twin-to-twin transfusion syndrome (TTTS), while risk factors of BI in these patients remains unknown. Our study aims to discern potential risk factors that contribute to BI in premature infants with TTTS.

Methods: We conducted a retrospective cohort and analyzed clinical data of premature infants diagnosed with TTTS at the Northwest Women's and Children's Hospital between January 1, 2015 and January 1, 2020. Data included the infants' perinatal information, key postnatal examinations, laboratory tests, and treatments.

Results: Of the 84 patients enrolled in the study, 22 (26.2%) were categorized in the BI group and 62 (73.8%) in the non-BI group, based on cranial imaging. No significant differences were found at baseline between the groups in relation to the proportion of males (40.9% *vs.* 35.5%, P=0.845), median gestational age (weeks) [31.9 (31.5, 33.4) *vs.* 34.2 (31.6, 35.4), P=0.061], average weight (g) (1,676.4±567.5 *vs.* 1,845.2±511.7, P=0.200), maternal age (years) [29.5 (26.0, 31.0) *vs.* 28.5 (27.8, 31.0), P=0.656], the proportion of *in-vitro* fertilization (9.1% *vs.* 16.1%, P=0.648), cesarean sections (86.4% *vs.* 93.5%, P=0.549) or TTTS donor infants (50.0% *vs.* 51.6%, P=0.897). Multivariate logistic regression analysis indicated that invasive mechanical ventilation [invasive mechanical ventilation (IMV); odds ratio (OR) =4.365; 95% confidence interval (CI): 1.066–17.870; P=0.040], [necrotizing enterocolitis (NEC); OR =8.632; 95% CI: 1.542–48.318; P=0.014], [single intrauterine fetal demise (sIUFD); OR =14.067; 95% CI: 1.298–224.421; P=0.031], and a 5-minute Apgar score <9 (OR =4.663; 95% CI: 1.015–21.419; P=0.048) were strongly associated with BI in TTTS premature infants.

Conclusions: Our study identifies IMV, NEC, sIUFD, and a 5-minute Apgar score <9 as independent risk factors for BI in premature infants with TTTS.

Keywords: Twin-to-twin transfusion syndrome (TTTS); premature infants; brain injury (BI)

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Introduction

Background

Brain injury (BI) in premature infants, comprising damage to white matter, neurons, and axons, is induced by perinatal adverse events. This broad category includes conditions such as periventricular leukomalacia (PVL), intraventricular hemorrhage (IVH), and subsequent hydrocephalus following hemorrhage, and affects 5% to 10% of premature cases (1,2).

Rationale and knowledge gap

BI is more prevalent in twin premature infants, notably

those with twin-to-twin transfusion syndrome (TTTS), with incidence ranging from 10% to 35% (3-5). BI substantially impairs the development of an infant's nervous system, potentially leading to severe cognitive and motor neural function disorders (6). This significantly impacts infants' quality of life and ability to care for themselves, places heavy psychological and financial strain on their families, and contributes to societal medical burdens. The lack of specific clinical manifestations makes early diagnosis of BI challenging (7), and current treatments are of limited and uncertain efficacy (8). As a result, the early identification of TTTS infants at high risk for BI, and the provision of timely interventions, are important clinical priorities.

Objective

This study aims to analyze this specific group of TTTS premature infants to identify risk factors for BI. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-387/rc).

Methods

Study population

We retrospectively collected clinical data from twin premature infants admitted to the Neonatal Intensive Care Unit (NICU) of Northwest Women's and Children's Hospital between January 1, 2015 and January 1, 2020. Inclusion criteria were: (I) diagnosis of TTTS; (II) admission to our unit within seven days post-birth; (III) availability of comprehensive clinical data; and (IV) gestational age <37 weeks. Exclusion criteria were: (I) both twins being stillborn; (II) gestational age <28 weeks; (III) the presence of severe congenital abnormalities, inborn metabolic disorders, or chromosomal anomalies; and (IV) infant mortality or discharge occurring within 72 hours after birth.

Highlight box

Key findings

- Invasive mechanical ventilation, necrotizing enterocolitis, single intrauterine fetal demise, and a 5-minute Apgar score <9 were identified as independent risk factors for brain injury (BI) in premature infants with twin-to-twin transfusion syndrome (TTTS).

What is known and what is new?

- BI is prevalent in premature infants with TTTS, with incidence rates varying from 10% to 35%. However, the lack of specific clinical manifestations makes early diagnosis of BI challenging. The early identification of infants at high risk for BI is an important clinical issue.
- This is the first study that reported risk factors for BI in premature infants with TTTS.

What is the implication, and what should change now?

- The factors identified in this study can be used to predict the risk of BI in preterm infants with TTTS.

Study design

Prenatal diagnosis and intervention for TTTS

Twin pregnant women underwent routine ultrasound examinations at our prenatal outpatient room. A TTTS diagnosis was made by obstetricians and radiologists collaboratively. Upon confirmation, an individualized treatment and follow-up plan was designed by a multidisciplinary team following meticulous evaluations.

Delivery room and NICU management

In the delivery room, a team of pediatricians and anesthetists were on standby, ready to provide immediate resuscitation to premature infants if necessary. Subsequently, patients were transferred to the NICU for additional monitoring and treatment.

Upon admission, all premature infants underwent routine tests, including a blood count, arterial blood gas analysis, and liver and kidney function tests. Cranial ultrasound examinations were conducted on the 3rd day after birth, with follow-up examinations on the 14th and 28th days as required. Treatment plans were developed by a team of professional doctors during infants' hospital stays. Infants with a gestational age <32 weeks or with suspected BI during ultrasound examinations underwent cranial magnetic resonance imaging (MRI) to further evaluate the presence of BI after the stable condition. Information mentioned above was obtained from the medical records and telephone calls.

Diagnostic criteria

TTTS was categorized based on the ultrasound staging system proposed by Quintero (9). The diagnosis of BI relied on the Papile diagnostic system (10), "Diagnostic suggestions for periventricular-intraventricular hemorrhage

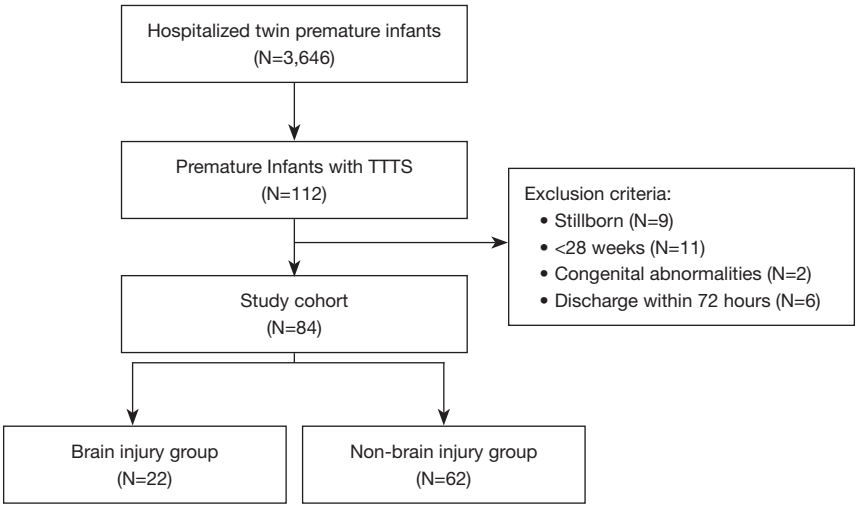

Figure 1 Patient flowchart. TTTS, twin-to-twin transfusion syndrome.

and periventricular leukomalacia in premature infants" (11), and the "Experts' consensus on the diagnosis, prevention and treatment of brain injury in premature infants in China" (12). The diagnostic criteria included: (I) IVH grades 3–4; (II) periventricular hemorrhagic infarction; (III) ventriculoperitoneal liquefaction; (IV) PVL grades II–III; (V) Ventriculomegaly; and (VI) cerebral edema. The existence of any of these manifestations in cranial imaging confirmed a BI diagnosis.

Study group

Based on the results of cranial imaging, infants were divided into two groups: those diagnosed with BI (BI group) and those without (non-BI group).

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Northwest Women's and Children's Hospital (approval number: 2022-055) and individual consent for this retrospective analysis was waived.

Statistical analysis

IBM SPSS Statistics (version 25.0; IBM Corp., Armonk, NY, USA) was utilized for statistical analyses. Continuous variables were reported as either median (interquartile range) or mean (standard deviation), and categorical variables were expressed as percentages. Student's *t*-test was deployed for comparing variables with normal distributions. The Mann-Whitney *U* test was employed for comparison of variables with non-normal distributions. Pearson's Chi-square (χ^2) test or Fisher's exact test was used to compare categorical variables. A two-tailed P value of <0.05 was deemed statistically significant.

Results

Patient characteristics

Screening of a total of 3,646 hospitalized twin premature infants resulted in the enrollment of 84 TTTS cases, with BI diagnosed in 22 cases (26.2%) and absent in 62 cases (73.8%) (*Figure 1*). The BI group comprised 1 case (1.2%) of grade III IVH, 2 cases (2.2%) of cerebral edema, and 19 cases (22.1%) of grade II or higher PVL. The median gestational age of diagnosis is 36.9 (35.1, 38.9) weeks. Of the entire cohort, 31 (36.9%) cases were male, 12 (14.3%) were conceived via *in-vitro* fertilization, 77 (91.7%) were delivered via cesarean section, and 41 (48.8%) were TTTS recipients. The median maternal age was 29.0 (27.0, 31.0) years, mean birth weight was 1,801.1±528.7 g, and the median gestational age was 33.4 (31.6, 35.1) weeks. The number of iatrogenic premature delivery was 54 (61.9%). There were no significant differences between the BI and non-BI groups for the variables mentioned above (*Table 1*).

Table 1 Demographic and clinical characteristics of TTTS premature infants

Variables	All patients (n=84)	BI group (n=22)	Non-BI group (n=62)	P
Birth weight (g)	1,801.1±528.7	1,676.4±567.5	1,845.2±511.7	0.200
Gestational age (weeks)	33.4 (31.6, 35.1)	31.9 (31.5, 33.4)	34.2 (31.6, 35.4)	0.061
Gender				0.845
Male	31 (36.9)	9 (40.9)	22 (35.5)	
Female	53 (63.1)	13 (59.1)	40 (64.5)	
Conception mode				0.648
In-vitro fertilization	12 (14.3)	2 (9.1)	10 (16.1)	
Natural	72 (85.7)	20 (90.9)	52 (83.9)	
Delivery mode				0.549
Vaginal delivery	7 (8.3)	3 (13.6)	4 (6.5)	
Cesarean section	77 (91.7)	19 (86.4)	58 (93.5)	
Reason for premature delivery				0.615
Spontaneous	32 (38.1)	7 (31.8)	25 (40.3)	
Iatrogenic	54 (61.9)	15 (68.2)	39 (59.7)	
Donor/recipient				0.897
Donor	43 (51.2)	11 (50.0)	32 (51.6)	
Recipient	41 (48.8)	11 (50.0)	30 (48.4)	
Age of mother (years)	29.0 (27.0, 31.0)	29.5 (26.0, 31.0)	28.5 (27.8, 31.0)	0.656

Data are presented as mean ± SD, median (IQR), or n (%). TTTS, twin-to-twin transfusion syndrome; BI, brain injury; SD, standard deviation; IQR, interquartile range.

Univariate analysis of perinatal factors

Significant differences between the BI and non-BI groups were observed in the following perinatal variables according to the univariate analysis: a 1-minute Apgar score <8 (72.7% *vs.* 30.6%, P=0.001), a 5-minute Apgar score <9 (86.4% *vs.* 38.7%, P<0.001), single intrauterine fetal demise (sIUFD) (18.2% *vs.* 1.6%, P=0.016), neonatal respiratory distress syndrome (NRDS) (63.6% *vs.* 35.0%, P=0.020), neonatal infection (50.0% *vs.* 14.5%, P=0.001), and necrotizing enterocolitis (NEC) (31.8% *vs.* 4.8%, P=0.003) (*Table 2*).

Univariate analysis of laboratory tests and treatment

Significant differences were observed in laboratory tests and treatment measures between the BI and non-BI groups, including partial pressure of arterial carbon dioxide ($PaCO_2$) >50 mmHg (45.5% *vs.* 21.0%, P=0.027), peripherally inserted central catheter or umbilical venous catheter (PICC/UVC) insertion (63.6% *vs.* 38.7%, P=0.044), and use of invasive mechanical ventilation (IMV) (45.5% *vs.* 11.3%, P=0.001) (*Table 3*).

Multivariate analysis

Variables with a P value <0.1 in the univariate analysis and baseline characteristics were incorporated into a multivariate logistic regression model. The model revealed that IMV [odds ratio (OR) =4.365; 95% confidence interval (CI): 1.066–17.870], NEC (OR =8.632; 95% CI: 1.542–48.318), sIUFD (OR =14.067; 95% CI: 1.298–224.421), and a 5-minute Apgar score <9 (OR =4.663; 95% CI: 1.015–21.419) were independent risk factors for BI in TTTS premature infants (*Table 4*). The Omnibus test demonstrated superior performance of the current model over the null model (P<0.001), and the Hosmer-Lemeshow test indicated a good fit of the model to the data (P=0.99).

Table 2 Univariate analysis of perinatal factors for BI in TTTS premature infants

Variables	BI group (n=22)	Non-BI group (n=62)	P
1-min Apgar score <8	16 (72.7)	19 (30.6)	0.001*
5-min Apgar score <9	19 (86.4)	24 (38.7)	<0.001*
Gestational hypertension/preeclampsia	3 (13.6)	3 (4.8)	0.371
Intrauterine infection	3 (13.6)	6 (9.7)	0.909
Intrauterine interventions	6 (27.3)	14 (22.6)	0.657
Laser ablation	4 (18.2)	12 (18.8)	0.796
Amnioreduction	2 (9.1)	2 (4.8)	0.598
Antenatal corticosteroid therapy	17 (77.3)	44 (71.0)	0.569
Fetal growth restriction	5 (22.7)	14 (22.6)	0.989
Umbilical cord abnormal	2 (9.1)	11 (17.7)	0.535
Placenta abnormal	4 (18.2)	15 (24.2)	0.788
sIUFD	4 (18.2)	1 (1.6)	0.016*
Neonatal asphyxia	2 (9.1)	3 (4.8)	0.842
NRDS	14 (63.6)	21 (35.0)	0.020*
Neonatal infection	11 (50.0)	9 (14.5)	0.001*
NEC	7 (31.8)	3 (4.8)	0.003*

Data are presented as n (%). *, P<0.05. BI, brain injury; TTTS, twin-to-twin transfusion syndrome; sIUFD, single intrauterine fetal demise; NRDS, neonatal respiratory distress syndrome; NEC, necrotizing enterocolitis.

Discussion

A number of studies have explored the risk factors for BI in premature infants. Factors such as sepsis, failure of prenatal hormone treatment, a 5-minute Apgar score <7, tracheal intubation, extremely low gestational age, respiratory distress syndrome, intrauterine infection, and hypercapnia have been implicated in BI (13,14). However, these investigations did not discriminate twin premature infants, TTTS premature infants, or other specific patient populations. Thus, the relevant clinical pathophysiological factors in these patients were not considered, potentially limiting the predictive value for these distinct groups. Furthermore, the incidence of BI tends to be higher in these particular subsets than in generic premature infants (3-5). Consequently, our study has concentrated on TTTS premature infants and ultimately identified IMV, NEC, sIUFD, and a 5-minute Apgar score <9 as independent risk factors for BI.

Mechanical ventilation serves as a critical therapeutic approach for premature infants in the NICU. Nonetheless, extensive cohort studies have shown that prolonged mechanical ventilation augments the risk of PVL in premature infants (15), and even low tidal volume or short-term mechanical ventilation might induce BI (16). This concurs with our observations (OR =4.365; 95% CI: 1.066–71.870). Mechanical ventilation can amplify the production of inflammatory markers, stimulate the activation of microglia and astrocytes, and ultimately lead to oligodendrocyte apoptosis and maturation disorder (17). It may also contribute to unstable cerebral blood flow, thereby increasing the risk of IVH (18). Hence, pediatricians should be vigilant of the risk for BI associated with mechanical ventilation and implement appropriate preventative strategies. These could include the early administration of pulmonary surfactants and enhancement of intrauterine lung maturation. Moreover, selection of suitable ventilator parameters tailored to the infant's condition may help minimize the use of invasive ventilation. Volume-targeted ventilation and appropriate oxygen saturation target (85–89%) after birth could reduce the duration of mechanical ventilation, stabilize cerebral blood flow and reduce the

Table 3 Univariate analysis of laboratory tests and treatment for BI in TTTS premature infants

Variables	BI group (n=22)	Non-BI group (n=62)	P
HGB (g/L)	159.5±47.4	169.5±53.4	0.440
Blood glucose at birth (mmol/L)	3.0±1.2	3.3±1.3	0.341
WBC ($\times10^9$/L)	9.6 [7.8, 16.3]	11.1 [8.3, 14.6]	0.053
PLT ($\times10^9$/L)	193.1±88.2	214.3±78.7	0.296
NEUT%	40.3±17.2	45.8±18.6	0.228
K^+ (mmol/L)	4.3 (4.1, 4.7)	4.5 (4.1, 4.8)	0.376
Na^+ (mmol/L)	140.5 (136.8, 142.0)	140.0 (137.6, 143.0)	0.450
Cl^- (mmol/L)	105.6 (103.7, 109.3)	108.0 (105.0, 110.3)	0.211
Albumin <28 g/L	5 (22.7)	20 (32.3)	0.401
pH >7.25	7 (31.8)	15 (24.2)	0.485
PaO_2 <60 mmHg	5 (22.7)	19 (30.6)	0.480
$PaCO_2$ >50 mmHg	10 (45.5)	13 (21.0)	0.027*
Pulmonary surfactant	9 (40.9)	14 (22.6)	0.098
Caffeine	9 (40.9)	18 (29.0)	0.305
Glucocorticoid	3 (13.6)	1 (1.6)	0.053
TPN >7 d	16 (72.7)	41 (66.1)	0.569
PICC/UVC	14 (63.6)	24 (38.7)	0.044*
Antibiotics >7 d	16 (72.7)	35 (56.5)	0.179
Meropenem	3 (13.6)	5 (8.1)	0.732
Vancomycin	0	2 (3.2)	1.000
Antifungal agents	3 (13.6)	6 (9.7)	0.909
IMV	10 (45.5)	7 (11.3)	0.001*

Data are presented as mean ± SD, median (IQR), or n (%). *, P<0.05. BI, brain injury; TTTS, twin-to-twin transfusion syndrome; HGB, hemoglobin; WBC, white blood cell; PLT, platelets; NEUT%, the percentage of neutrophils; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; TPN, total parenteral nutrition; PICC, peripherally inserted central catheter; UVC, umbilical venous catheter; IMV, invasive mechanical ventilation; SD, standard deviation; IQR, interquartile range.

Table 4 Multivariate logistic regression for BI in TTTS premature infants

Variables	b	S.E.	Wald χ^2	P	OR	95% CI
IMV	1.474	0.719	4.199	0.040	4.365	1.066–17.870
NEC	2.155	0.879	6.016	0.014	8.632	1.542–48.318
sIUFD	2.837	1.315	4.658	0.031	14.067	1.298–224.421
5-min Apgar score <9	1.540	0.788	3.917	0.048	4.663	1.015–21.419
Constant	–2.958					

BI, brain injury; TTTS, twin-to-twin transfusion syndrome; S.E., standard error; OR, odds ratio; CI, confidence interval; IMV, invasive mechanical ventilation; NEC, necrotizing enterocolitis; sIUFD, single intrauterine fetal demise.

incidence of BI (19,20).

NEC is a severe, multi-etiological, systemic gastrointestinal disease characterized by robust inflammation and high mortality rates, predominantly afflicting premature infants (21). This study identified NEC as an independent risk factor for BI in TTTS premature infants (OR =8.632; 95% CI: 1.542–48.318; P=0.014). Kidokoro *et al.* (22) reported that infants diagnosed with stage II or higher NEC demonstrated an increased risk of grade 3/4 IVH or PVL. Similarly, Garg *et al.* (23) observed that 50% of NEC-afflicted premature infants subjected to surgery sustained BI. NEC provokes a systemic inflammatory response and triggers the release of cytokines, leading to neuronal damage via the activation of microglia, stimulation of inflammatory pathways, and compromise of the blood-brain barrier (23-25). Therefore, the main measurements to prevent BI include the prevention and appropriate treatment of NEC. Receipt of mother's own breast milk and adequate anti-infective therapy can effectively prevent the occurrence of NEC (26). Controlling intestinal inflammation, removing infected and necrotic intestinal tissue and optimizing nutritional management can improve outcomes of premature infants with NEC (27). Meanwhile, routine surveillance of brain function and implementation of brain imaging techniques are imperative.

In twin pregnancies, the incidence of sIUFD is estimated to be around 6% (28). Disturbingly, BIs may afflict as many as 36% of the surviving offspring (29). Cruciat and Gijtenbeek (29,30) reported that hemodynamic fluctuations induced by blood reperfusion in the surviving fetus may lead to multicystic encephalomalacia, infarction, and eventual neurological dysfunction. Ann I. Scher and colleagues (31) found that, in cases where sIUFD occurred, the risk of cerebral palsy in the surviving twin quadrupled in comparison to standard twin births. Echoing this, our research demonstrated that sIUFD indeed constitutes an independent risk factor for BI in TTTS premature infants (OR =14.067; 95% CI: 1.298–224.421). Therefore, the focus may be prevention of sIUFD or minimizing its harm. If the development of twins was seriously discordant or one fetus was severely congenital malformation, fetal reduction should be performed as soon as possible to decrease the risk of IVH and other adverse outcomes (32). When sIUFD occurs in early pregnancy, whether it is associated with significant deleterious effects on the surviving twin is debatable (33). When sIUFD occurs after 32 weeks, it is recommended to terminate pregnancy. Timely cesarean section can prevent the occurrence of acute TTTS and its complications (34). Meanwhile, careful monitoring of the surviving fetus via ultrasound throughout the pregnancy is crucial. Further, conducting a cranial MRI examination immediately post-birth can aid in the proactive prevention, diagnosis, and treatment of potential BI (29,35).

A number of studies have reported a low Apgar score as a risk factor for BI in premature infants (36-38). In many of these studies, a 5-minute Apgar score was deemed a risk factor, with the risk threshold typically ranging between 4 and 7 (22,39). These findings underscore that premature infants unable to promptly recover from asphyxiation or hypoxia via medical interventions are at a substantially increased risk of developing BI. Nonetheless, our study revealed that among TTTS twin premature infants, a 5-minute Apgar score of <9 may still present a risk for BI. This finding that is in line with the results of a prospective cohort study by Persson *et al.* (40). Therefore, for high-risk premature infants, it remains essential to maintain close monitoring and provide high-quality resuscitation according to "Neonatal Resuscitation Algorithm" of American Heart Association Guidelines. Additionally, for participants who have been trained in neonatal resuscitation, training should occur periodically that supports retention of knowledge, skills, and behaviors (41).

The two primary intrauterine approaches to management of TTTS are laser ablation and amnioreduction. In this cohort, a total of 24 infants received intrauterine interventions, including 20 cases of laser ablation and 4 cases of amnioreduction. Laser ablation was applied in 4 (18.2%) and 12 (18.8%) infants, and amnioreduction was applied in 2 (9.1%) and 2 (4.8%) infants in BI and non-BI group, respectively. However, these two variables showed no difference between the two groups in univariate analysis (P=0.796, P=0.598). Laser ablation is a common intervention of TTTS, but whether it could decrease the risk of BI is controversial. Some studies showed significantly lower neurodevelopmental impairment than after symptomatic therapy (42,43). However, in other studies, almost all of the risk of BI in survivors is due to complications related to preterm birth, rather than a direct result of TTTS or laser therapy (44-46). Considering that laser ablation can prevent many other adverse outcomes of TTTS, it should be actively implemented for patients with indications.

Limitations

As a single-center retrospective study, this research might encompass some selection bias. The sample size is

constrained due to the relatively low incidence of TTTS premature infants, which limits the scope of our findings. Future investigations should aim to expand the case number or undertake prospective studies to further elucidate these findings.

Conclusions

IMV, NEC, sIUFD, and a 5-minute Apgar score <9 were identified as independent risk factors for BI in TTTS premature infants.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-387/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-387/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-387/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Northwest Women's and Children's Hospital (approval number: 2022-055) and individual consent for this retrospective analysis was waived.

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