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Increased risk of retinopathy of prematurity in donors with twin-to-twin transfusion syndrome: a cohort study

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Short Title: Donor Status as a Risk Factor for Retinopathy of Prematurity

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Keywords Retinopathy of prematurity; Twin to twin transfusion syndrome; Monochorionic twins; Neonatal outcome.

What does this study add to current knowledge?

- Twin-to-twin transfusion syndrome (TTTS) is associated with increased perinatal mortality and morbidity rates, especially in donors. Whether TTTS donors are also more at risk for developing retinopathy of prematurity (ROP) is not well known.
- Within-pair analysis showed TTTS donors to have a two-fold increased risk for any stage ROP and severe ROP compared to recipients.
- Donor status, lower gestational age at birth and increased duration of mechanical ventilation are independent risk factors for any stage ROP in monochorionic twins with TTTS.

What are the main clinical implications?

- Our study emphasizes the need for risk profile enhancement and increased awareness for ROP in TTTS donors, especially those with a lower gestational age at birth and longer duration of mechanical ventilation, and the necessity for acknowledgement in counseling.

Abstract

Introduction The purpose of this study was to evaluate the within-pair difference in retinopathy of prematurity (ROP) between donors and recipients with twin-to-twin transfusion syndrome (TTTS) and to identify risk factors for ROP development.

Methods This retrospective cohort study included 147 TTTS twin pairs managed between 2002-2022 and eligible for ROP screening. Primary outcomes were any stage ROP and severe ROP. Secondary outcomes were hemoglobin at birth, red blood cell transfusions, mechanical ventilation days, postnatal steroids and neonatal morbidity. Donor status was defined as having polyhydramnios pre-laser.

Results Rates of any stage ROP (23% vs. 14%) and severe ROP (8% vs. 3%) were significantly higher in donors compared to recipients. Donors received a higher number of blood transfusions (1 (±1.9) vs. 0.7 (±1.5)). Five factors were univariately associated with any stage ROP: donor status (odds ratio (OR) 1.9; 95% CI 1.3–2.9), lower gestational age (GA) at birth (OR 1.7; 95% CI 1.4–2.1), small for GA (OR 2.1; 95% CI 1.3–3.5), mechanical ventilation days (OR 1.1; 95% CI 1.1–1.2) and blood transfusions in phase 1 (OR 2.3; 95% CI 1.2–4.3). Three factors were independently associated with any stage ROP: donor status (OR 1.8; 95% CI 1.1–2.9), lower GA at birth (OR 1.6; 95% CI 1.2–2.1) and mechanical ventilation days (OR 1.1, 95% CI 1.0–1.1). Donor status was univariately associated with severe ROP (OR 2.3, 95% CI 1.1–5.0).

Conclusion Any stage ROP and severe ROP are detected twice as frequently in donors compared to recipients. Increased awareness for ROP is needed in donors, especially those with lower GA at birth and longer duration of mechanical ventilation.

Introduction

Retinopathy of prematurity (ROP), a vasoproliferative retinal disorder, is a severe disease affecting 10-25% of all premature infants screened for ROP [1]. This leading cause of childhood blindness is essentially due to abnormal retinal vessel development, occurring in two phases. In phase I, retinal hyperoxia exposure leads to attenuation and cessation of retinal vessel growth due to decreased levels of insulin-like growth factor-1 (IGF-1), caused by placental disruption, and decreased levels of vascular endothelial growth factor (VEGF). In phase II, abnormal retinal vessel growth following increased VEGF concentrations occurs due to retinal hypoxia and increased IGF-1 levels [2,3]. Proangiogenic factors IGF-1 and VEGF are crucial for retinal vessel growth and are decreased in infants with a gestational age (GA) at birth <32 weeks or a birthweight <1500 grams [1]. Besides GA and birthweight, prolonged mechanical ventilation, sepsis, perforated necrotizing enterocolitis (NEC) and postnatal corticosteroids are also included in the ROP screening criteria [4]. Anemia, red blood cell transfusions and growth restriction are also risk factors of ROP [5-7].

A small study has shown that twin-to-twin transfusion syndrome (TTTS) survivors have a higher risk of ROP development and progression compared to neonates without TTTS, matched for GA and birthweight [8]. TTTS is a complication affecting 10-15% of monochorionic twin pregnancies [9]. The pathophysiology of TTTS is primarily due to imbalance of inter-twin blood flow through placental anastomoses, leading to hypovolemia with oliguria and oligohydramnios in donors and hypervolemia with polyuria and polyhydramnios in recipients [10]. TTTS is associated with increased perinatal mortality and morbidity rates, with even higher rates when left untreated [11,12].

TTTS donors suffer more often from fetal anemia and are more often growth restricted than recipients, which might implicate that donors are at increased risk of developing ROP [13]. The within-pair risk difference is still unknown, since data on this topic is scarce [14,15]. Hence, this study aims to investigate the within-pair difference in ROP between donors and recipients and to identify risk factors for ROP development in TTTS twins in order to further adjust the risk profile for ROP screening.

Methods

Study design

This retrospective cohort study was conducted according to STROBE guidelines and approved by the METC Leiden-Den Haag-Delft (G20.004) [16]. All monochorionic twin pairs with TTTS managed and delivered at Leiden University Medical Center, the national referral center for fetal therapy, between 2002 and 2022 who met ROP screening criteria were eligible for inclusion. TTTS pairs were excluded when only one twin was eligible for ROP screening or when single/double intrauterine fetal demise occurred. Additionally, twin pairs with missing data on donor/recipient status or ROP screening were excluded. TTTS diagnosis was based on the Eurofoetus criteria and was classified according to the Quintero staging [17,18]. ROP diagnosis was based on the International Classification of ROP (ICROP 2) which categorizes severity in five stages, location of retinal involvement in three zones and presence of plus disease [19]. Eligibility for ROP screening was based on the Dutch screening guideline and was defined as GA at birth <32.0 weeks and/or birthweight <1500 grams [19]. The first ROP screening was performed five weeks after birth, but not before 31 weeks post menstrual age. A within-pair comparison between donor and recipient was performed.

Data collection

The following perinatal TTTS and ROP baseline characteristics and neonatal outcomes were collected from digital medical records: Quintero staging, TTTS treatment (fetoscopic laser therapy, amnioreduction, no therapy), complete TTTS fetoscopic laser therapy (i.e. no residual vascular anastomoses), GA at laser, caesarean delivery, sex, GA at birth, birthweight, small for gestational age (SGA) (birthweight <10th centile) [20], donor/recipient status (twin with polyhydramnios/ oligohydramnios pre-laser), ROP staging (most severe stage included) [19], ROP requiring laser treatment, any stage ROP, severe ROP (≥ stage 3, laser treatment, plus disease and/or aggressive posterior ROP), hemoglobin level at birth (g/dL), red blood cell transfusion, number of red blood cell transfusions, red blood cell transfusion in phase I (i.e. <34.0 weeks GA) [6,21], red blood cell transfusion in phase II (i.e. ≥34.0 weeks GA), duration of mechanical ventilation (days), postnatal corticosteroids, sepsis (positive bacterial blood culture) and NEC ≥ stage 2 [22]. Red blood cell transfusions in phase I of ROP may increase the risk of ROP, while transfusions in phase II, beginning in week 32-34, might decrease this risk. Therefore, we have set the limit of phase I to 34.0 weeks to ensure that the potential negative effect of red blood cell transfusions in phase I of ROP will not influence our outcome data of phase II.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA). Data are presented as median with interquartile ranges (IQR), mean with standard deviation (SD), n/N (%) or odds ratio (OR) with 95% confidence interval (CI). Cases with missing data for variables were excluded from analysis. Generalized Estimating Equations were used to test for association between donor/recipient status and outcomes. Univariate regression analysis was performed to identify potential predictors of ROP. The following variables, based on literature, were studied in risk factor analysis: donor status, complete TTTS laser, GA at birth, SGA, mechanical ventilation and blood transfusion in phase I. A correlation analysis was performed to detect substantial correlations among predictors. When multicollinearity was present, only one predictor was included. Subsequently, significant associations found in univariate analysis were included in multivariate regression analysis. P-values <0.05 were considered statistically significant.

Results

Between 2002 and 2022, a total of 394 TTTS pairs managed and delivered at our center were eligible for ROP screening. After applying our exclusion criteria (n=247), 147 TTTS pairs were eligible for analysis (Figure 1).

Baseline characteristics of all included TTTS cases are presented in Table 1. This cohort was delivered at a median GA at birth of 29.6 (28.3–30.7) weeks with a median birthweight of 1242 (994–1447) grams. Donors had a lower birthweight of 1105 (915–1330) grams compared to 1350 (1100–1515) grams in recipients. A total of 35% (104/294) neonates were SGA, with higher SGA rates in donors (54%, 79/147) compared to recipients (17%, 25/147). Most TTTS cases were classified as Quintero stage II and III (29% (42/146) and 44% (65/146), respectively), and 82% (121/147) were treated with fetoscopic laser surgery. Neonatal death did not occur in this cohort.

In Table 2, the characteristics of ROP cases are summarized. ROP occurred in 18% (54/294), with most cases classified as mild ROP (70%, 38/54). Five cases classified as mild ROP had missing data on ROP staging. Eight neonates with ROP stage 2 were classified as severe ROP due to having plus disease or receiving laser treatment. Nine ROP

cases required laser treatment, including two cases with ROP stage 2. The majority of ROP cases were treated with fetoscopic laser surgery (83%, 45/54), including 85% (29/34) of donors and 80% (16/20) of recipients. The median GA at laser was 27.0 (18.0–24.0) weeks in neonates with any stage ROP and 27.0 (20.0–24.9) weeks in neonates with severe ROP. Twenty-seven ROP cases were classified as Quintero stage III or IV, including 16 donors and 11 recipients. Donor twins with ROP had a lower birthweight of 972 (766–1133) grams compared to 1025 (896–1183) grams in recipients. Neonates with severe ROP were delivered at an earlier GA of 27.9 (25.4–28.9) weeks with a lower birthweight of 856 (666–1142) grams compared to any stage ROP (GA: 28.1 (26.9–29.7) weeks and birthweight: 987 (776–1155) grams).

Any stage ROP was detected more frequently in donors than in recipients, 23% (34/147) versus 14% (20/147) respectively (p=0.002). Fifteen twin pairs presented with ROP in both donor and recipient. Donors were also at increased risk for severe ROP, namely 8% (11/147) versus 3% (5/147) in recipients (p=0.036). The rate of SGA was higher in donors (54%) than in recipients (17%) (p<0.001). A total of 38% (51/135) of donors received red blood cell transfusions compared to 30% (40/135) of recipients (p=0.076). The mean number of red blood cell transfusions was higher in donors (1.0 ±1.9) versus recipients (0.7 ±1.5) (p=0.007). Neonatal outcomes of donors and recipients in TTTS twins are shown in Table 3. Except for ROP, SGA and number of blood transfusions, no other within-pair differences were found.

Univariate and multivariate regression analyses were performed (Table 4). In the univariate analysis, five factors were significantly associated with any stage ROP: donor status (OR 1.9; 95% CI 1.3–2.9), lower GA at birth (OR 1.7; 95% CI 1.4–2.1), SGA (OR 2.1; 95% CI 1.3–3.5), mechanical ventilation days (OR 1.1; 95% CI 1.1–012) and red blood cell transfusion in phase I (OR 2.3; 95% CI 1.2–4.3). After multivariate analysis, donor status (OR 1.8; 95% CI 1.1–2.9), lower GA at birth (OR 1.6; 95% CI 1.2–2.1) and mechanical ventilation days (OR 1.1, 95% CI 1.0–1.1) were independently associated with any stage ROP. Additional univariate analysis for severe ROP (n=16) also showed donor status to be significantly associated (OR 2.3, 95% CI 1.1–5.0).

Discussion

This retrospective cohort study in TTTS survivors showed that donors have a two-fold increased risk for any stage ROP compared to recipients. Any stage ROP and severe ROP were detected more frequently in donors. Risk factor analysis showed that donor status, lower GA at birth and longer duration of mechanical ventilation were independently associated with any stage ROP.

Two previous studies have also explored the differences in ROP between donors and recipients in TTTS twins, but showed no significant difference [8,23]. The retrospective cohort study by Halvorsen et al. focused on liveborn TTTS twins treated with fetoscopic laser surgery and showed a similar incidence of severe ROP (defined as ROP stage ≥3) in donors and recipients (4.9% vs. 6.5%, respectively) [23]. Gschließer et al., who explored the association between TTTS and the development of ROP in twins eligible for ROP screening, also showed a similar incidence of ROP (defined as ROP ≥stage 1 and/or plus disease) in donors and recipients (83.3% vs. 81.8%, respectively) [8]. Notably, our methods of analysis differed considerably from the above-mentioned studies. While those studies analyzed the general difference between donors and recipients, our study examined the ROP risk within twin pairs. Additionally, our study had a relatively large sample size (N=294) compared to Halvorsen et al. (N=88) and Gschließer et al. (N=17) and, therefore, provides stronger evidence.

The cause of the higher risk of ROP occurrence and progression in donor twins is unknown. Hypothetically, several mechanisms can be envisaged. Donors with TTTS are at increased risk of fetal anemia which may induce dysregulation of proangiogenic factors and therefore pose a higher risk for ROP. On the other hand, recipients experience cardiac strain, due to hypervolemia, with subsequent hypoxia that may also increase proangiogenic factors. In both TTTS twins, significant higher concentrations of VEGF have been found compared to uncomplicated twin pregnancies [24]. However, no significant intertwin difference in serum VEGF concentrations was found.

Since fetal anemia occurs more frequently in donors, the donor twin is more likely to have lower fetal and/or neonatal hemoglobin levels at birth and to receive red blood cell transfusions. No significant difference was found in hemoglobin at birth between donors and recipients in our study, but this is essentially due to laser treatment of the majority of our cohort. Nevertheless, donors received blood transfusions more often than recipients during admission, probably due to their higher risk of anemia. Multiple red blood cell transfusions have been shown to increase the odds of ROP [25]. However, the timing of red blood cell transfusions is crucial when determining this

association. In our study, red blood cell transfusions in phase I were univariately associated with any stage ROP (p=0.009) and showed a trend towards increased incidence in donors compared to recipients (p=0.077). While red blood cell transfusions in the vaso-obliterative phase I can have a negative effect on retinal vessel growth, red blood cell transfusions in the vasoproliferative phase II, beginning around 32-34 weeks of gestation, have the opposite effect [21].

Furthermore, a shorter transfusion free survival after birth is associated with a higher risk of severe ROP [6]. Remarkably, higher concentrations of fetal hemoglobin during the first week decreases the risk of ROP [26]. Red blood cell transfusions mainly consist of adult hemoglobin levels. Adult hemoglobin has a lower affinity for oxygen compared to fetal hemoglobin and higher concentrations enhance the ability of red blood cells to release oxygen to tissues and end organs [27]. Therefore, a decrease of fetal hemoglobin and an increase of adult hemoglobin will increase oxygen availability to the retina, which may induce phase I of ROP [28].

Another factor that may explain the higher risk of ROP in the TTTS donors is a lower birthweight. Interestingly, in monochorionic twins with selective fetal growth restriction (sFGR), the smaller twin appears to be more at risk for ROP compared to its appropriately grown co-twin [29]. In singletons, preterm SGA infants also have increased odds of ROP [7]. The association between SGA and ROP might be explained by the increased rates of mechanical ventilation and neonatal complications in SGA infants [30,31]. Since TTTS donors are also more likely to be SGA than their co-twin, donors could therefore be at increased risk for ROP in analogy to our results and sFGR twins [32].

Mechanical ventilation is also associated with any stage ROP and severe ROP. Prolonged mechanical ventilation is an independent risk factor for ROP and is included in the ROP screening criteria [33,34]. Neonates receiving mechanical ventilation >7 days have a two-fold increased odds of ROP [4]. Prolonged mechanical ventilation is associated with severe neonatal morbidity and increased risk for ROP in both singleton and twin cohorts [35,36]. Interestingly, twins receiving invasive mechanical ventilation had a higher ROP rate compared to singletons and was even higher in neonates with a birthweight <1500 grams [35]. Duration of mechanical ventilation has also been identified as an independent risk factor for any stage ROP in our TTTS cohort.

Finally, premature neonates are at increased risk for severe neonatal morbidities and mortality, especially when complicated with TTTS [11]. Lower GA at birth <30 weeks is the main independent risk factor in the Dutch ROP screening program together with birthweight <1250 grams [34]. The NEDROP cohorts, which mainly consist of singletons born in 2009 and 2017, had lower rates of any stage ROP (2009: 19.5% and 2017: 20.4%) and severe ROP (2009: 1.8% and 2017: 3.3%) compared to our donors (23.1% and 7.5%, respectively) [37]. TTTS twins are generally born prematurely and are therefore more at risk for ROP. Lower GA at birth is also an independent risk factor in our cohort. The median GA at birth (29.6 weeks) in our TTTS cohort is lower compared to most centers, as we only included twin pairs that were eligible for ROP screening (<32 weeks and/or 1500 grams). Since our study design focused on within-pair differences between donor and recipient, prematurity was eliminated as a confounder for the increased ROP rate in donors, considering that both twins have the same GA at birth.

The main limitation of this study is its retrospective design, which may have introduced bias. Additionally, the small sample size of severe ROP hampered risk factor analysis beyond donor status. Moreover, long term visual outcomes of ROP were lacking. Studies focusing on long-term follow-up in TTTS twins have shown that the incidence of blindness (bilateral) does not differ between donors and recipients [38-42]. However, this may be due to early intervention and successful ROP screening. Nevertheless, this study provides new insight in ROP development in TTTS twins in a relatively large cohort. Furthermore, by analyzing the within-pair differences in risk for ROP, essential confounders such as GA at birth were eliminated.

In conclusion, this study shows that TTTS donors have a two-fold increased risk for any stage ROP and severe ROP compared to recipients. Besides the donor status, we found lower GA at birth and increased duration of mechanical ventilation to be independently associated with an increased risk for any stage ROP. Larger retrospective and prospective studies are required to validate these findings. Finally, standardized long-term follow-up should be implemented to assess the long-term visual outcomes in donor twins. This can help us further improve the risk profile for ROP in order to ensure a more favorable neonatal outcome. Nevertheless, our study emphasizes the need for risk profile enhancement and extra awareness for ROP in TTTS donors, especially those with a lower GA at birth and longer duration of mechanical ventilation. Furthermore, increased risk for ROP in TTTS donors should be acknowledged in counseling.

Statement of Ethics

Study approval statement: This study protocol was reviewed and approved by the Medical Ethics Committee METC Leiden-Den Haag-Delft with the approval number G20.004.

Consent to participate statement: The Medical ethical committee METC Leiden-Den Haag-Delft waived the requirement for informed consent due to its retrospective design.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Author Contributions

Salma El Emrani, Lotte E. van der Meeren, Nicoline E. Schalij-Delfos and Enrico Lopriore conceived and designed the study. Salma El Emrani, Sophie G. Groene, Jip A. Spekman and Enrico Lopriore acquired data. Salma El Emrani, Sophie G. Groene, Femke Slaghekke, Nicoline E. Schalij-Delfos and Enrico Lopriore contributed to data analysis and interpretation. Salma El Emrani wrote the original draft. All authors critically reviewed the manuscript and provided approval of the final publication. Nicoline E. Schalij-Delfos and Enrico Lopriore supervised the project.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Fig. 1. Flowchart of study inclusion. Abbreviations: TTTS, Twin-twin transfusion syndrome; ROP, retinopathy of prematurity; IUFD, intrauterine fetal death.

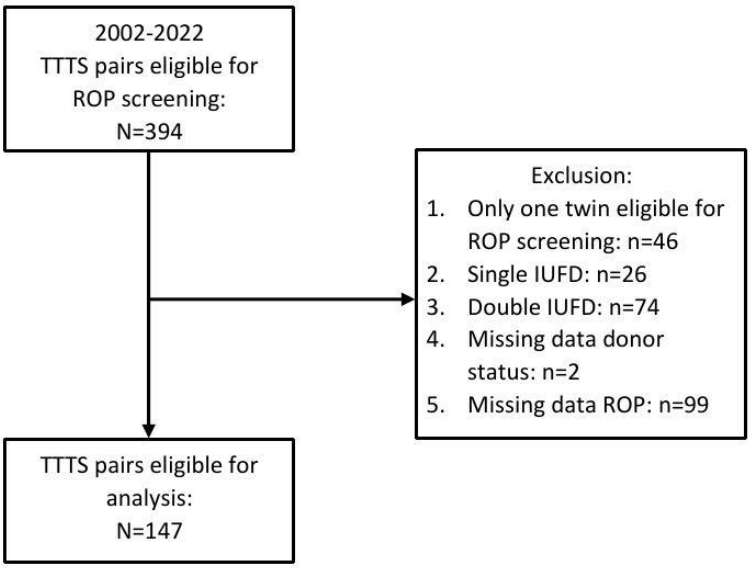

Table 1. Baseline characteristics of included TTTS cases.

Characteristics	Total cohort (N=294 neonates from 147 TTTS pregnancies)
Quintero stage - %	
I	31/146 (21)
II	42/146 (29)
III	65/146 (45)
IV	8/146 (5)
V	0/146 (0)
TTTS treatment - %	
Laser	121/147 (82)
Amnioreduction	16/147 (11)
No therapy	10/147 (7)
TTTS laser complete - %	75/103 (73)
Gestational age at laser - weeks	20.0 (17.0–24.0)
Caesarean delivery - %	90/145 (62)
Male - %	132/294 (45)
Gestational age at birth - weeks	29.6 (28.3–30.7)
Birthweight - grams	1242 (994–1447)
SGA - %	104/294 (35)

Data are presented as median (IQR) and n/N(%). Abbreviations: TTTS, Twin-twin transfusion syndrome; SGA, small for gestational age.

Table 2. Baseline characteristics of TTTS cases with any stage ROP.

Characteristics	Any stage ROP (N=54)	Donor (N=34)	Recipient (N=20)
ROP Staging - %*			
Stage 1	15/49 (31)	8/30 (27)	7/19 (37)
Stage 2	26/49 (53)	17/30 (57)	9/19 (47)
Stage 3	5/49 (10)	3/30 (10)	2/19 (11)
Stage 4	2/49 (4)	1/30 (3)	1/19 (5)
Stage 5	1/49 (2)	1/30 (3)	0/19 (0)
ROP requiring laser - %	9/54 (17)	6/34 (18)	3/20 (15)
Gestational age at laser - weeks	20.7 (18.0–24.0)		
Gestational age at birth - weeks	28.1 (26.9–29.7)		
Birthweight - grams	987 (776–1155)	972 (766–1133)	1025 (896–1183)
SGA - %	22/54 (41)	18/34 (53)	4/20 (20)

Data are presented as median (IQR) and n/N(%). Abbreviations: ROP, retinopathy of prematurity; SGA, small for gestational age. *Four donors and one recipient were classified as mild ROP, but their specific ROP stage was not reported.

Table 3. Comparison of neonatal outcomes between donor and recipient in TTTS twins.

Characteristics	Donor (N=147)	Recipient (N=147)	p-value
Any stage ROP - %	34/147 (23)	20/147 (14)	**0.002**
Severe ROP - %	11/147 (8)	5/147 (3)	**0.036**
SGA	79/147 (54)	25/147 (17)	**<0.001**
Hemoglobin at birth - g/dL*	15.7 (±3.8)	16.5 (±3.4)	0.141
RBC transfusion - %	51/135 (37.8)	40/135 (29.6)	0.076
Number of RBC transfusions - n*	1.0 (±1.9)	0.7 (±1.5)	**0.007**
1	19/135 (14)	19/135 (14)	
≥2	32/135 (24)	21/135 (16)	
RBC transfusion in phase I - %	44/129 (34)	33/129 (26)	0.077
RBC transfusion in phase II - %	4/126 (3)	1/126 (1)	0.213
Duration of mechanical ventilation - days*	0 (0–3)	0 (0–4)	0.531
Postnatal steroids - %	5/122 (4)	3/122 (3)	0.323
Sepsis - %	21/122 (17)	28/122 (23)	0.263
NEC ≥2 - %	6/147 (4)	7/147 (5)	0.739

Data are presented as mean (±SD), median (IQR) and n/N(%). Abbreviations: TTTS, Twin-twin transfusion syndrome; ROP, retinopathy of prematurity; SGA, small for gestational age; RBC, red blood cell; NEC, necrotizing enterocolitis. *Missing data occurred in variables with N<147 and 4 cases had missing data on hemoglobin at birth, 12 on number of RBC transfusions and 26 on mechanical ventilation.

Table 4. Risk factor analysis for any stage ROP.

Characteristics	Any stage ROP (N=54)	No ROP (N=240)	Univariate analysis OR (95% CI)	SE	p-value	Multivariate analysis OR (95% CI)	SE	p-value
Donor vs. recipient status								
Donor - %	34/54 (63)	114/240 (48)	1.9 (1.3–2.9)	0.214	**0.002**	1.8 (1.1–2.9)	0.261	**0.030**
Laser complete vs. incomplete								
Incomplete laser -%	14/41 (34)	42/165 (25)	1.5 (0.6–3.8)	0.467	0.371	-	-	-
Gestational age at birth - weeks	28.1 (26.9–29.7)	29.8 (28.6–30.7)	1.7 (1.4–2.1)	0.107	**<0.001**	1.6 (1.2–2.1)	0.138	**0.001**
SGA - %	22/54 (41)	82/240 (34)	2.1 (1.3–3.5)	0.250	**0.002**	1.7 (0.9–3.3)	0.325	0.091
Mechanical ventilation - days	3.0 (0–7.3)	0 (0–3.0)	1.1 (1.1–1.2)	0.024	**<0.001**	1.1 (1.0–1.1)	0.033	**0.042**
RBC transfusion in phase I - %	21/45 (47)	62/220 (28)	2.3 (1.2–4.3)	0.318	**0.009**	0.9 (0.4–2.0)	0.380	0.857

Data are presented as n/N(%), median (IQR) and odds ratio (95% confidence interval). Abbreviations: ROP, retinopathy of prematurity; SGA, small for gestational age; RBC, red blood cell.