Fetal Diagnosis and Therapy

Research Article

Fetal Diagn Ther 2020;47:800–809
DOI: 10.1159/000509032

Received: September 5, 2019
Accepted: May 26, 2020
Published online: July 31, 2020

Survival Outcomes by Fetal Weight Discordance after Laser Surgery for Twin-Twin Transfusion Syndrome Complicated by Donor Fetal Growth Restriction

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Keywords

Laser · Selective intrauterine growth restriction · Selective reduction · Twin growth discordance · Twin-twin transfusion syndrome

Abstract

Introduction: Management options for treatment of twin-twin transfusion syndrome (TTTS) with severe donor intrauterine growth restriction (IUGR) include fetoscopic laser surgery and umbilical cord occlusion (UCO). We studied perinatal survival outcomes in this select group after laser surgery, stratifying patients by preoperative estimated fetal weight (EFW) discordance. ***Methods:*** In this retrospective study of monochorionic diamniotic twin gestations with TTTS and selective donor IUGR who underwent laser surgery (2006–2017), preoperative EFW discordance was calculated ([(larger twin − smaller twin)/(larger twin)] × 100) and cases were divided into discordance strata. Severe EFW discordance was defined as >35%. The primary outcome was 30-day donor twin neonatal survival. ***Results:*** The 371 cases were distributed by discordance strata: ≤20% (74 [19.9%]), 21–25% (49 [13.2%]), 26–30% (68 [18.3%]), 31–35% (53 [14.3%]), 36–40% (51 [13.7%]), 41–45% (38 [10.2%]), >45% (38 [10.2%]). Donor 30-day survival declined as the discordance strata increased: 86.5, 85.7, 83.8, 75.5, 64.7, 63.2, and 65.8% ($p = 0.0046$); 30-day survival was inversely associated with severe discordance (>35%) (64.6 vs. 83.2%, $p < 0.0001$). ***Discussion:*** In TTTS cases complicated by donor IUGR with severe growth discordance, laser surgery was associated with donor survivorship greater than 60% suggesting that, in this setting, laser surgery remains a reasonable alternative treatment to UCO.

Introduction

Twin-twin transfusion syndrome (TTTS) occurs in 10–20% of monochorionic twin gestations and is caused by unequal sharing of blood through placental arteriovenous anastomoses between the donor and recipient twin

Previously presented: Portions of the manuscript were presented in Abstract #218, Poster Session 1, at the Society for Maternal-Fetal Medicine, 39th Annual Pregnancy Meeting, Las Vegas, NV, from February 11 to February 16, 2019.

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[1, 2]. Selective laser photocoagulation of communicating vessels (SLPCV) is the preferred treatment for TTTS [3–5]. In some studies, it has been reported that more than 50% of TTTS cases are concurrently complicated by donor twin selective intrauterine growth restriction (IUGR), defined as estimated fetal weight (EFW) of the donor twin <10th percentile for gestational age (GA) [6–8].

Studies have suggested that donor twin intrauterine fetal demise (IUFD) after laser surgery for TTTS is increased among those with IUGR and/or abnormal preoperative Doppler waveforms [8–11]. In addition, increased perinatal mortality in monochorionic pregnancies is associated with EFW discordance [12–16]. Preoperative growth discordance may increase the risk of perinatal mortality in TTTS patients who undergo SLPCV [9, 17]. Snowise et al. [17] reported that EFW discordance of >30% was associated with postoperative donor IUFD (OR 7, 95% CI 2–23, donor death in 29% of cases); where both growth discordance and preoperative umbilical artery (UA) reversed end diastolic flow (REDF) were present, all donors underwent IUFD.

In lieu of SLPCV treatment, some centers offer selective termination of the growth restricted donor twin to TTTS patients with severe growth discordance, IUGR, and/or fetal Doppler waveform abnormalities. The rationale for this treatment is to maximize the survivorship of the recipient twin when the donor is determined to have a high likelihood of demise, while minimizing the risk of preterm premature rupture of membranes and/or preterm delivery by utilizing smaller diameter surgical instruments than are needed for laser treatment [18, 19]. Although preoperative donor twin IUGR is a risk factor for fetal demise, it remains unclear whether there is a threshold of discordance beyond which postoperative donor demise is highly likely. The objective of this study was to examine perinatal survival in TTTS patients complicated by donor IUGR, stratifying patients by preoperative EFW discordance.

Materials and Methods

We performed a retrospective cohort study of all consecutive monochorionic diamniotic twin gestations that underwent SLPCV for TTTS from 2006 to 2017. All patients underwent a preoperative comprehensive ultrasound examination, including the assessment of fetal anatomy, Doppler waveforms, amniotic fluid maximum vertical pocket, and cervical length. TTTS was diagnosed if the amniotic fluid maximum vertical pocket measured ≤2 cm in the donor's sac and ≥8 cm in the recipient's sac. Patients were classified prospectively according to the Quintero staging system [20] and were offered SLPCV with or without sequential technique between 16 and 26 gestational weeks [21]. Patients are counseled that at our center umbilical cord occlusion (UCO) is performed for TTTS on a case-by-case basis, and preoperative fetal growth restriction or severe growth discordance itself is not a routine indication for UCO. UCO for TTTS is generally reserved for cases with contraindications to SLPCV (i.e., significant membrane separation, subchorionic hematoma, and proximate cord insertions).

The study cohort was composed of patients with TTTS treated with SLPCV, who were concurrently diagnosed with preoperative donor IUGR. Donor IUGR was diagnosed with TTTS when the donor EFW measured <10th percentile (Hadlock) for the GA [22]. Patients with both twins having EFW <10th percentile (dual IUGR) were excluded from the study because they would have been classified into the reference group, as nondiscordant. Preoperative EFW discordance was calculated as follows: ([(larger twin – smaller twin)/(larger twin)] × 100). For study purposes, patients were stratified based on preoperative EFW discordance into the following groups: ≤20, 21–25, 26–30, 31–35, 36–40, 41–45, and >45%. The reference group was defined as EFW discordance ≤20% and severe discordance was defined as >35%. Exclusion criteria included gestations with any of the following: triplet and higher order multiples, preoperative septostomy, more than 1 laser surgery, selective termination, or pregnancy termination.

In the first month following surgery, we recommended that the referring perinatologists perform weekly ultrasound examinations assessing fetal membranes, amniotic fluid levels, and Doppler waveforms. Thereafter, we recommended ultrasound examinations every 2–3 weeks, with the additional charge of assessing fetal growth.

Prospectively collected data included maternal demographics, perioperative data, and delivery outcomes. Delivery outcomes were obtained prospectively by the research team via acquisition of medical records and telephone inquiry of the referring providers and the patient. The "donor" and "recipient" status of the twins was verified to the best of our ability using clinical information such as pre-delivery EFW, fetal positions, and delivery order. Patient characteristics and outcome data were described by the discordance strata and tested bivariately with the primary outcome. The primary outcome was 30-day donor twin survival; all other outcomes were considered secondary. IUFD was defined as absence of fetal cardiac activity by ultrasonography prior to delivery, and neonatal demise (NND) was defined as postnatal death within the first 30 days of life.

Analyses of categorical variables were performed using the χ^2 test or with Fisher exact test where appropriate. Continuous variables were compared with the Wilcoxon rank Sum test or Kruskal-Wallis test. Patient characteristics associated with 30-day donor survival ($p < 0.05$) were considered statistically significant. Multiple logistic regression models were used to examine the association between EFW discordance and the dichotomous outcome (30-day donor survival) in the presence of covariates of interest. All analyses were performed using SAS statistical software (version 9.3). Results are reported as median (range). All patients provided informed consent. This study was approved by the Institutional Review Board of the University of Southern California for the Health Sciences campus.

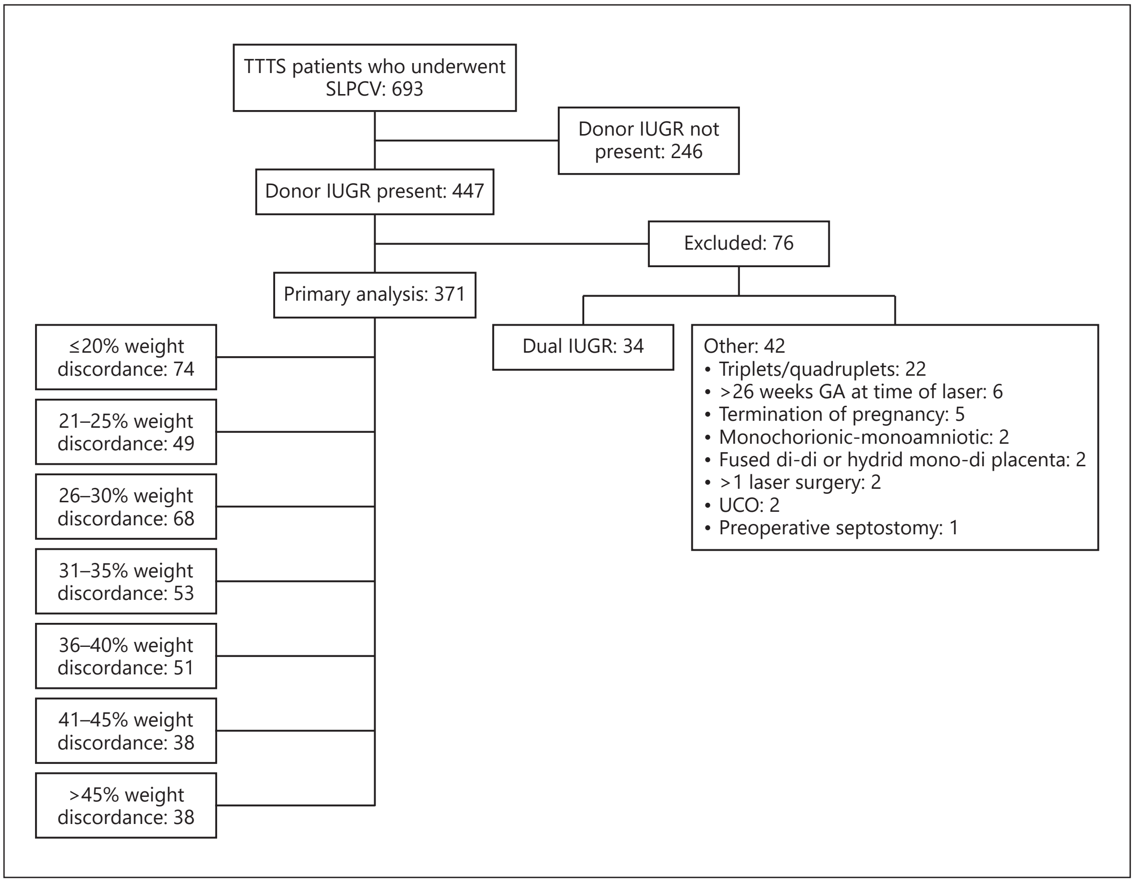

Fig. 1. Flowchart of the patients with TTTS during the study period. TTTS, twin-twin transfusion syndrome; SLPCV, selective laser photocoagulation of communicating vessels; IUGR, intrauterine growth restriction; GA, gestational age; UCO, umbilical cord occlusion.

Results

Six hundred ninety-three patients underwent SLPCV for TTTS during the study period (Fig. 1). Of these, 447 patients had preoperative TTTS and donor IUGR. A total of 76 patients were excluded, including 34 for dual IUGR. Two patients underwent UCO for proximate placental cord insertion sites (<2 cm) due to concern for an increased risk of dual demise secondary to thermal injury to the cord roots if SLPCV were to be attempted.

The study cohort consisted of 371 patients who had donor IUGR and TTTS and underwent SLPCV (Fig. 1). The number of patients within each EFW discordance stratum was as follows: ≤20% (74 [19.9%]), 21–25% (49 [13.2%]), 26–30% (68 [18.3%]), 31–35% (53 [14.3%]), 36–40% (51 [13.7%]), 41–45% (38 [10.2%]), and >45% (38 [10.2%]).

Patient characteristics by discordance stratum are detailed in Table 1. Compared to the reference group of EFW discordance ≤20%, bivariate analysis demonstrated a higher percentage of advanced Quintero stage (III/IV) TTTS patients in the greater weight discordance groups ($p < 0.0001$). In addition, preoperative donor UA absent end-diastolic flow and REDF were statistically more common in the EFW discordant groups. GA at surgery was not significantly different among groups. There was a significantly higher rate of donor IUFD within the greater EFW discordant groups.

The proportion of donors with postoperative IUFD was significantly higher in those with severe EFW discordance (>35%) than in those with ≤35% discordance (38/127 [29.9%] vs. 36/244 [14.8%], $p = 0.0009$). The median number of days from surgery to donor IUFD in the severe EFW discordance group ($n = 38$) was 17.0 (range 0–109) days. Of these 38, 17 (44.7%) and 2 (5.3%) died

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Table 1. Patient characteristics stratified by preoperative EFW discordance percentage

Patient characteristics	Preoperative EFW discordance, %							p value
	≤20%, $N = 74$	21–25%, $N = 49$	26–30%, $N = 68$	31–35%, $N = 53$	36–40%, $N = 51$	41–45%, $N = 38$	>45%, $N = 38$	
Maternal age, years	29.0 (18–42)	30.0 (17–41)	29.0 (17–43)	29.0 (16–43)	30.0 (16–40)	29.5 (18–43)	27.0 (15–47)	0.5614
Multiparous	51 (68.9%)	35 (71.4%)	42 (61.8%)	29 (54.7%)	28 (54.9%)	20 (52.6%)	18 (47.4%)	0.1347
GA at surgery, weeks	20.6 (16.4–25.3)	21.1 (17.4–25.4)	19.7 (16.4–25.1)	19.6 (16.7–26.0)	20.1 (16.9–24.9)	19.9 (17.0–24.1)	20.6 (17.7–24.6)	0.0756
Cerclage	10 (13.5%)	2 (4.1%)	9 (13.2%)	9 (17.0%)	5 (9.8%)	6 (15.8%)	6 (15.8%)	0.5095
Quintero stage								
I	14 (18.9%)	8 (16.3%)	11 (16.2%)	10 (18.9%)	10 (19.6%)	3 (7.9%)	1 (2.6%)	0.0002
II	23 (31.1%)	17 (34.7%)	8 (11.8%)	12 (22.6%)	7 (13.7%)	3 (7.9%)	2 (5.3%)	
III	35 (47.3%)	23 (46.9%)	43 (63.2%)	24 (45.3%)	29 (56.9%)	27 (71.1%)	28 (73.7%)	
IV	2 (2.7%)	1 (2.0%)	6 (8.8%)	7 (13.2%)	5 (9.8%)	5 (13.2%)	7 (18.4%)	
Quintero stage III or IV	37 (50.0%)	24 (49.0%)	49 (72.1%)	31 (58.5%)	34 (66.7%)	32 (84.2%)	35 (92.1%)	<0.0001
Preoperative UA AEDF, donor	9 (12.2%)	7 (14.3%)	23 (33.8%)	22 (41.5%)	23 (45.1%)	21 (55.3%)	27 (71.1%)	<0.0001
Preoperative UA REDF, donor	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3.9%)	5 (13.2%)	6 (15.8%)	<0.0001
Preoperative EFW, g, donor	285 (125–615)	296 (143–626)	222 (112–561)	225 (113–549)	198 (102–518)	198 (101–477)	183 (114–538)	<0.0001
Preoperative EFW, g, recipient	327 (150–698)	389 (184–825)	315 (156–807)	330 (167–800)	336 (164–839)	348 (171–805)	395 (214–1,076)	0.1063
Postoperative day 1 IUFD								
Donor	2 (2.7%)	2 (4.1%)	1 (1.5%)	4 (7.5%)	3 (5.9%)	4 (10.5%)	3 (7.9%)	0.3743
Recipient	1 (1.4%)	2 (4.1%)	1 (1.5%)	1 (1.9%)	0 (0%)	1 (2.6%)	1 (2.6%)	0.8499
Any postoperative IUFD								
Donor	8 (10.8%)	6 (12.2%)	10 (14.7%)	12 (22.6%)	14 (27.5%)	13 (34.2%)	11 (28.9%)	0.0157
Recipient	7 (9.5%)	5 (10.2%)	25 (7.4%)	2 (3.8%)	4 (7.8%)	1 (2.6%)	1 (2.6%)	0.5790

The reference group is EFW discordance ≤20%. p values represent the overall comparison of all groups using the Kruskal-Wallis test. Results are expressed as median (range) or n (%). EFW, estimated fetal weight; GA, gestational age; UA, umbilical artery; AEDF, absent end-diastolic flow; REDF, reversed end-diastolic flow; IUFD, intrauterine fetal demise.

Table 2. Delivery and neonatal outcomes stratified by preoperative EFW discordance

Patient characteristics	Preoperative EFW discordance, %							p value
	≤20%, N = 74	21–25%, N = 49	26–30%, N = 68	31–35%, N = 53	36–40%, N = 51	41–45%, N = 38	>45%, N = 38	
GA at delivery, weeks	34.0 (21.1–39.9)	34.3 (20.3–39.4)	34.6 (18.6–40.4)	34.0 (19.3–39.7)	33.7 (20.0–38.7)	33.2 (20.4–37.6)	33.1 (24.7–40.1)	0.5962
Delivery mode								
Cesarean	51 (68.9%)	34 (69.4%)	46 (67.6%)	39 (73.6%)	40 (78.4%)	27 (71.1%)	29 (76.3%)	0.8031
Vaginal	21 (28.4%)	15 (30.6%)	22 (32.4%)	13 (24.5%)	11 (21.6%)	10 (26.3%)	9 (23.7%)	
Both	2 (2.7%)	0 (0%)	0 (0%)	1 (1.9%)	0 (0%)	1 (2.6%)	0 (0%)	
Birth weight difference, %[a]	6.4 (0.0–27.4)	9.3 (1.2–37.5)	15.2 (0.6–60.1)	26.4 (0.8–73.2)	28.6 (0.4–66.8)	28.2 (0.5–66.0)	41.2 (8.9–76.6)	<0.0001
NICU admission[b]								
Donor	47 (71.2%)	30 (69.8%)	41 (70.7%)	35 (85.4%)	30 (81.1%)	24 (96.0%)	26 (96.3%)	0.0093
Recipient	49 (73.1%)	30 (68.2%)	42 (66.7%)	39 (76.5%)	34 (72.3%)	32 (86.5%)	26 (70.3%)	0.4635
NND[b]								
Donor	2 (3.0%)	1 (2.3%)	1 (1.7%)	1 (2.4%)	4 (10.8%)	1 (4.0%)	2 (7.4%)	0.3458
Recipient	0 (0%)	2 (4.5%)	3 (4.8%)	1 (2.0%)	1 (2.1%)	2 (5.4%)	2 (5.4%)	0.5979
30-day survivor								
Donor	64 (86.5%)	42 (85.7%)	57 (83.8%)	40 (75.5%)	33 (64.7%)	24 (63.2%)	25 (65.8%)	0.0046
Recipient	67 (90.5%)	42 (85.7%)	60 (88.2%)	40 (94.3%)	46 (90.2%)	35 (92.1%)	35 (92.1%)	0.8357
30-day survivors, n								
0	3 (4.1%)	2 (4.1%)	4 (5.9%)	2 (3.8%)	4 (7.8%)	2 (5.3%)	1 (2.6%)	0.2538
1	11 (14.9%)	10 (20.4%)	11 (16.2%)	12 (22.6%)	15 (29.4%)	13 (34.2%)	14 (36.8%)	
2	60 (81.1%)	37 (75.5%)	53 (77.9%)	39 (73.6%)	32 (62.7%)	23 (60.5%)	23 (60.5%)	

The reference group is EFW discordance ≤20%. p values represent the overall comparison of all groups using the Kruskal-Wallis test. Results are expressed as median (range) or n (%). EFW, estimated fetal weight; GA, gestational age; IUFD, intrauterine fetal demise; NICU, neonatal intensive care unit; NND, neonatal demise. [a] Eighty-eight patients were removed from the original denominator of 371 due to IUFD of either the donor or recipient. [b] Seventy-four donors and 25 recipients were removed from the original denominator of 371 due to IUFD and not included in neonatal outcomes.

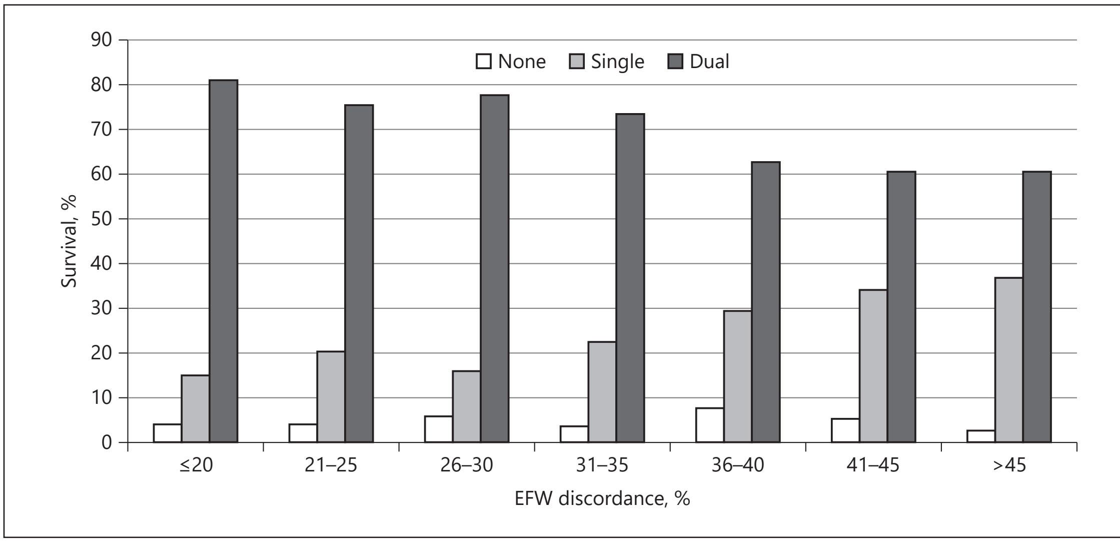

Fig. 2. The 30-day survivorship by preoperative fetal weight discordance strata. EFW, estimated fetal weight.

within the first and second postoperative weeks, respectively. Of the 74 donor IUFD in the entire denominator, 35 (47.3%) occurred within 1 week after surgery, and a total of 41 (55.4%) occurred within 2 weeks. The median GA at delivery for pregnancies not complicated by donor IUFD was 34.0 weeks (range 23.7–39.9), compared to 34.7 weeks (range 18.6–40.4) for pregnancies with donor IUFD in all growth discordance strata ($p = 0.1938$).

Delivery data and 30-day neonatal outcomes are displayed in Table 2. The delivery GA and mode of delivery were not statistically different across EFW discordance strata. Neonatal intensive care unit admission varied across discordance strata for the donor, but not recipient, twin. Among live-born donor fetuses, the proportion of those experiencing NND was higher in those with severe EFW discordance than in the others (7/89 [7.9%] vs. 5/208 [2.4%], $p = 0.0479$). Recipient IUFD and NND did not differ. Donor 30-day survival declined with each increasing EFW discordance stratum (respectively): 86.5% (reference), 85.7, 83.8, 75.5, 64.7, 63.2, and 65.8%, $p = 0.0046$. Similarly, 30-day dual survivorship was lower with increasing EFW discordance, although this did not meet statistical significance: 81.1% (reference), 75.5, 77.9, 73.6, 62.8, 60.5, and 60.5%, $p = 0.0689$ (Fig. 2). The dual 30-day survival was lower in those with severe discordance of >35% than in those with less discordance (78/127 [61.4%] vs. 189/244 [77.5%], $p = 0.0015$).

Bivariate analysis was performed to compare those with and without 30-day donor survivors (Table 3). Patients with 30-day donor survivors were less likely to have severe EFW discordance (82/285 [28.8%] vs. 45/86 [52.3%], $p < 0.0001$). In a multiple logistic regression model adjusted for maternal age, multiparity, Quintero stage, and GA at surgery, and using the ≤20% stratum as a reference, the higher discordance strata were less likely to be associated with donor survival: discordance 36–40% (OR 0.32; 95% CI: 0.13–0.78; $p = 0.0128$), discordance 41–45% (OR 0.31; 95% CI: 0.12–0.83; $p = 0.0198$), and discordance >45% (OR 0.33; 95% CI: 0.12–0.88; $p = 0.0262$). Last, patients with severe (>35%) EFW discordance compared to patients with ≤35% discordance were less likely to have a 30-day donor survivor (OR 0.39; 95% CI: 0.23–0.66; $p = 0.0004$) and dual 30-day survivors (OR 0.50; 95% CI: 0.30–0.81; $p = 0.0051$).

Discussion

Although preoperative donor twin IUGR and growth discordance are risk factors for fetal demise in TTTS patients, there are few data regarding the ideal treatment modality in the most severe cases. In our study, dual 30-day survival was lower in those with severe discordance of >35% than in those with less discordance. However, within each discordance stratum, at least 60% of the study population had dual survival, even those with >45% discordance in weight. Recipient survival ranged from 85.7 to 94.3% and did not vary with discordance ($p = 0.8357$).

Table 3. Patient characteristics associated with 30-day survival of the donor twin

Patient characteristics	30-day survivorship of donor		p value
	Yes, N = 285	No, N = 86	
Maternal age, years	29.0 (15–47)	30.0 (18–43)	0.7183
Race			
Asian	19 (6.7%)	8 (9.3%)	0.6056
Black	8 (2.8%)	2 (2.3%)	
Hispanic	93 (32.6%)	33 (38.4%)	
White	143 (50.2%)	39 (45.3%)	
Others	11 (3.9%)	1 (1.2%)	
Unknown	11 (3.9%)	3 (3.5%)	
GA at surgery, weeks	20.6 (16.4–26.0)	19.4 (17.0–24.6)	0.0020
Multiparous	167 (58.6%)	86 (65.1%)	0.3157
Cerclage	35 (12.3%)	12 (14.0%)	0.7121
Quintero stage			
I	50 (17.5%)	7 (8.1%)	0.0017
II	61 (21.4%)	11 (12.8%)	
III	145 (50.9%)	64 (74.4%)	
IV	29 (10.2%)	4 (4.7%)	
Preoperative UA AEDF			
Donor	84 (29.5%)	48 (55.8%)	<0.0001
Recipient	6 (2.1%)	0 (0%)	0.3430
Preoperative UA REDF			
Donor	3 (1.1%)	10 (11.6%)	<0.0001
Recipient	2 (0.7%)	0 (0%)	1.0000
EFW percent discordance	29.0 (0–66)	37.0 (10–56)	<0.0001
Discordance >35%	82 (28.8%)	45 (52.3%)	<0.0001
GA at delivery, weeks	34.0 (23.7–39.9)	33.9 (18.6–40.4)	0.5291
Birth weight, g			
Donor	1,652 (450–3,056)[a]	540 (270–1,050)[b]	<0.0001
Recipient	2,020 (575–4,438)[c]	2,211 (514–4,020)[d]	0.0145
Birth weight percent discordance	14.8 (0.0–73.2)	43.1 (1.9–76.6)	0.0117

Results are expressed as median (range) or *N* (%). *p* values represent comparison of variables present in surviving twins versus non-surviving twins. GA, gestational age; IUGR, intrauterine growth restriction; UA, umbilical artery; AEDF, absent end-diastolic flow of the umbilical artery; REDF, reversed end-diastolic flow; EFW, estimated fetal weight. [a] Total *N* = 285, after removal of donor twin IUFD cases to reflect the median birth weight of live-born neonates. [b] Total *N* = 12, after removal of donor twin IUFD cases to reflect the median birth weight of live-born neonates. [c] Total *N* = 35, after removal of recipient twin IUFD cases to reflect the median birth weight of live-born neonates. [d] Total *N* = 11, after removal of recipient twin IUFD cases to reflect the median birth weight of live-born neonates.

Donor 30-day survival did significantly decrease with increasing EFW discordance, with a range of 63.2–65.8% survival in the 3 greatest discordance strata (>35%). Severe discordance (>35%) was significantly associated with advanced Quintero stage (stage III or IV) (79.5 vs. 57.8%, $p < 0.0001$) and abnormal donor preoperative UA absent end-diastolic flow (55.9 vs. 25.0%, $p < 0.0001$) and UA REDF (10.2 vs. 0%, $p < 0.0001$).

Postoperative IUFD of the donor twin was more common in the increasingly discordant groups. One potential explanation for this finding is that there is likely to be unequal placental sharing between these twins, with placental insufficiency of the donor twin [23]. Donor NND was also significantly more common in the severely discordant twins, although it was a relatively rare occurrence with only 12 donor NND in our cohort (2.7%).

Previous studies have reported that discordant growth of dichorionic and monochorionic twins (with or without TTTS) may be a risk factor for adverse perinatal outcomes, including preterm delivery, neonatal intensive care unit admission, IUFD, and NND [12, 24–27]. The threshold for growth discordance varied in these studies, ranging from EFW differences greater than 10% to greater than 30%, with greater than 20% used as a common definition and the threshold for this study. However, a standard definition of fetal growth discordance does not currently exist, although a large retrospective study of 300,000 twin pregnancies (chorionicity data were unavailable) identified 20% as a potential threshold for increased risk of IUFD and neonatal death [28].

Previously, Snowise et al. [17] found that a growth discrepancy of >30% was associated with postoperative donor demise in a large prospective cohort study of TTTS patients treated with SLPCV. The study included all TTTS monochorionic twin gestations; dual IUGR patients were not excluded. This group created a receiver operating characteristic curve and reported an optimal cutoff of 30% discordance for prediction of donor demise, with a specificity of 72% and donor death occurring in 29% of cases above this threshold. Both our study and the study of Snowise et al. suggest that greater values of discordance can increase the risk of postoperative donor demise. However, the data do not support automatically proceeding with UCO for gestations with discordance and donor IUGR as the indications. In our study, decreased donor survival was associated with >35% discordance; however, 65.8% of donor twins still survived even with a discordance of >45%. Hence, while the risk of fetal death increased with growth discrepancy in TTTS pregnancies with IUGR present, there did not appear to be a clear EFW discordance threshold to guide physicians regarding when SLPCV should no longer be offered as a management option.

In complicated monochorionic pregnancies where it is anticipated that one fetus will die in utero, selective reduction may be considered a management option, where the goal is to optimize the survivorship of the remaining singleton. Co-twin survival rates were reported in TTTS neonates (67.3–76.8%) in a recent meta-analysis of selective reduction performed by radiofrequency ablation or bipolar cord occlusion [29], which may be explained by the underlying pathological effects of TTTS on the recipient twin. Others have described the use of UCO for severe growth discordance in non-TTTS cases [30, 31]. Our recipient survival rate after laser surgery was 90.3% (335/371), while our dual survival rate was at least 60% in the most discordant group. Thus, laser surgery affords at least equitable survival of the recipient twin as compared to UCO, with the benefit of a reasonable survival rate of the donor twin.

While there does not appear to be a definitive growth discordance threshold that is associated with survival after SLPCV for these patients, additional questions remain regarding predictive factors for donor twin demise. Incorporating abnormal umbilical artery or vein Doppler waveforms into a predictive model may aid in counseling regarding risk of demise. Furthermore, data on long-term health outcomes for former donor twins are limited. Previous studies have demonstrated donor twin catch-up growth after SLPCV, both in utero and during the first 2 years of life [32, 33]. These data suggest that the perinatal outcomes of growth-restricted donors may improve after SLPCV despite the presence of other preoperative risk factors of donor demise. Also, it is possible that this phenomenon of "catch-up" growth following SLPCV contributed to decreasing the frequency and severity of donor twin growth restriction later in gestation, and thus having less impact on delivery timing as demonstrated by similar GA at delivery in patients with and without donor IUFD (34.7 vs. 34.0 weeks, median). However, additional research is needed to determine if the degree of catch-up growth is related to the severity of growth restriction of the donor twins and what long-term impact this discrepancy has on the quality of life.

A strength of our study was that it was one of the largest cohorts of TTTS patients complicated by donor IUGR and treated with SLPCV that has been examined. Because of the large number of patients, we were able to further stratify them by preoperative weight discordance group, which has not been previously described. Snowise et al. [17] found >30% discordance to be a risk factor for demise: there were 52 patients with an EFW discordance of >30%. Whereas in our study, we included 180 patients with a preoperative EFW discordance of >30%, allowing us to further describe the survival outcomes in more narrow strata. There exists a clinical spectrum of EFW discordance in practice, and the stratified outcomes may enhance patient counseling in the future. Furthermore, this study was conducted at a single institution, allowing consistency in perioperative evaluation and surgical technique. Last, UCO was performed in only 2 patients during the study period, with the remainder undergoing SLPCV as the sole treatment regardless of the severity of disease, resulting in a uniformly treated patient population.

Limitations of the study are discussed. First, the majority of patients returned to the referring provider after SLPCV was performed; postsurgical and delivery management differences could have affected the outcomes. Postoperative donor IUFD occurred up to 109 days after surgery, with a median of 17 days. Postoperative management could have affected delivery timing and route, although differences in prenatal management were less likely to contribute to the IUFD rate, given that nearly half of the IUFD occurrences (n = 35, 47.3%) were within 1 week after surgery. Second, there is no standard definition of severe growth discordance, and thus, our findings may not be applicable in centers where different discordance categorizations or criteria exist. Third, short-term [34, 35] and long-term [36–38] morbidities associated with small for GA status (birth weight <10th percentile for GA) were not assessed. In particular, neurological outcomes were not assessed in this study. We have previously found that preoperative head circumference percentiles were associated with overall cognitive performance at 2 years of age [39]. Smaller preoperative head circumference identified children at risk of lower but still within normal range cognitive performance. Further research is needed to assess the impact of donor twin restriction on neurodevelopment, as this information is important for patient counseling. Furthermore, we excluded cases with dual IUGR, and therefore, these results may not apply to cases where both donor and recipient IUGR are present.

Even in cases of TTTS complicated by severe growth discordance, dual survival was 61.4% and donor survival was 64.6%. Thus, compared to SLPCV, it does not appear that selective reduction is a clearly advantageous management option for survival in TTTS patients with donor IUGR, regardless of the degree of inter-twin growth discordance. Further studies are needed to evaluate neurodevelopmental morbidity and other long-term outcomes. SLPCV remains a reasonable treatment option for TTTS gestations, even when donor IUGR and severe growth discordance are present.

Statement of Ethics

Our research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. All subjects have given their written informed consent. The study protocol was approved by the Institutional Review Board of the University of Southern California and complied with all patient protection criteria and ethical policies stipulated therein. The IRB approval number is HS-IRB#: HS-16-00468.

Conflict of Interest Statement

Dr. L.M.K. assists with research studies as an independent contractor. The other authors have nothing to disclose. No external financial support was received for this work.

Funding Sources

The authors did not receive any funding.

Author Contributions

L.C.G., A.H.C., L.M.K., D.A.M., and R.H.C. provided significant contributions to the writing of the manuscript. A.L., L.C.G., and A.H.C. were involved with data collection. L.M.K. provided statistical support. All authors reviewed the final version of the manuscript.

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