Use of internet-based surveys to collect long-term pediatric outcomes in patients with twin-twin transfusion syndrome treated with fetoscopic laser photocoagulation: A Prospective Observational Study

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Abstract

Background: In the U.S., patients with monochorionic diamniotic (MCDA) twins who undergo in-utero fetoscopic laser photocoagulation (FLP) for twin-twin transfusion syndrome (TTTS) may travel great distances for care. After delivery, many parents cannot return to study sites for formal pediatric evaluation due to geographic location and cost.

Objective: To collect long-term pediatric outcomes in patients who underwent FLP for TTTS.

Methods: We assessed the feasibility of using an internet-based survey designed in REDCap to collect parent-reported outcomes in children treated for TTTS at a single center during 2011-2019. Patients with ? 1 neonatal survivor were invited via email to complete three possible questionnaires: CSQ, child status questionnaire; FCQ, fetal center questionnaire; ASQ®-3, ages and stages questionnaire; M-CHAT-R/F,? modified checklist for autism in toddlers; TYQ, thank you questionnaire. The R programming language was used to automate survey distribution, scoring and creation of customized reports. The survey was performed in 2019 and repeated after 12 months in 2020.

Results: A total of 389 patients in 26 different states and 2 international locations had an email address on file and received an invitation in 2019 to complete the survey (median pediatric age 48.9 months [range 1.0 – 93.6]). Among surveyed mothers in 2019, the overall response rate was 37.3%, and the questionnaire completion rate was 98%, 87.8%, 71.1%, 86.4% and 74.3% for the CSQ, FCQ, ASQ®-3, M-CHAT-R/F and TYQ respectively. In 2020, the overall response rate was 57.8%, and the questionnaire completion rate was 96.4%, 91.1%, 86.1%, 91.7% and 80.4% for the CSQ, FCQ, ASQ®-3, M-CHAT-R/F and TYQ respectively.

Conclusions: This is the first study to employ both REDCap and computer automation to aid in the dissemination, collection and reporting of surveys to collect long-term pediatric outcomes in the field of fetal medicine.

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Keywords: Automation; survey; questionnaire; fetal medicine; pediatric outcomes; long-term outcomes;

Introduction

Background

Twin-to-Twin Transfusion Syndrome (TTTS) results from unbalanced vascular communications in a shared placenta between monochorionic diamniotic (MCDA) twins. Bidirectional vascular communications are present in up to 95% of MCDA twins and allow for a single, shared circulatory system.[1] However, in 9-15% of MCDA twins, unbalanced vascular communications produce a pathological state in which one fetus (the donor twin) over-transfuses the co-twin (the recipient).[2,3] Compensatory mechanisms result in progressive recipient polyhydramnios (excess amniotic fluid) and donor oligohydramnios (low amniotic fluid). Expectant management of this condition results in a mortality rate greater than 70%, typically due to sequelae from circulatory overload, compensatory hormonal dysfunction and/or preterm delivery due to worsening polyhydramnios.[4] The gold-standard treatment for TTTS is intra-uterine fetoscopic placental laser photocoagulation (FLP), which halts the abnormal blood exchange and yields better outcomes.[5] Despite this therapy, twins who survive TTTS may experience major disability at birth likely secondary to hemodynamic changes that occur in utero and/or sequelae of prematurity, as the average gestational age at delivery is approximately 32 weeks.[6] However, long-term outcomes for these surviving twins in the United States remain understudied, largely because of the logistical challenges of following patients who traveled far from home for treatment.

Prior work

The data on long-term pediatric outcomes in patients who undergo FLP for TTTS come almost entirely from centers outside the United States. Centers with a local and homogeneous referral base are more likely to report in-person pediatric evaluations,[7-10] although telephone and mail-in surveys have also been reported.[9,11,12] To date, there have been no attempts to collect long-term pediatric outcomes using internet-based methods in the field of fetal surgery.

In the United States, patients referred for treatment of TTTS may travel upwards of 2000 miles to receive care at a tertiary center of excellence.[13] The majority of these patients will travel home post-procedure and deliver at remote sites, which makes tracking neonatal and long-term outcomes challenging. At our center, thanks to considerable efforts from full-time research staff to collect maternal delivery and neonatal discharge records from patients' delivering hospitals, we have reported on the immediate and short-term neonatal complications (from time of delivery until hospital discharge) in patients who undergo FLP for TTTS.[14] However, prospectively collected in-person long-term follow-up of twins born after FLP in the U.S. would be exceedingly challenging and resource intensive. Therefore, internet-based collection methods may provide a viable approach.

Goal of This Study

The primary outcome of this study was to assess the feasibility of using computer automation to obtain, to the fullest extent, long-term pediatric outcomes from patients who underwent FLP for TTTS at a Fetal Center (FC) over a 2-year period.

Methods

Study Design

This was a cohort study of patients who were referred to the UTHealth Houston Fetal Center in Houston, Texas and who underwent FLP for TTTS between 2011 and 2019. Eligible patients were identified retrospectively from a registry of patients treated at our center who had previously consented to prospective follow-up of short-term maternal and neonatal outcomes (HSC-MS-10-0059). Approval was obtained from the Institutional Human Research Ethics Committee (HSC-MS-19-0363), and the study was conducted between June 1, 2019 and September 30, 2020.

Patients with TTTS who underwent FLP at our center during the study period and had both an email address on file and at least one surviving child from a monochorionic pair at time of neonatal hospital discharge were eligible for participation in this study. Exclusion criteria included patients without a registered email, or cases of dual fetal or neonatal demise.

Patient Recruitment and Consent

Patients who received the survey via email were instructed to follow a hyperlink to an online REDCap consent form, where details regarding study participation and confidentiality were provided. After giving e-consent, patients were emailed copies of the study protocol and directed to a subsequent child survival status questionnaire (CSQ). After indicating the survival status of both the ex-donor and the ex-recipient twins, the user was directed to a queue of online questionnaires, specific to the number of surviving children and their age.

Questionnaires

We designed research surveys in REDCap, a HIPAA-compliant, secure research data collection tool which can be used to distribute online, mobile-friendly surveys. Surveys consisted of three pediatric age–specific questionnaires distributed via email to consenting parents.

First, all participating patients were sent the **Child Status Questionnaire (CSQ)**, a series of 2-4 questions for each child which provided confirmation of child status as alive, demised in-utero (fetal demise) or demised after birth (neonatal demise). Based on user input indicating both the number of surviving children and pediatric age, specifically designed computer algorithms automatically tailored the number and type of survey questionnaires. Participating parents were sent any questionnaires applicable to their child's pediatric age.

The **Fetal Center Questionnaire (FCQ)** was adapted from a prior publication of long-term outcomes in twin gestations and was applicable to every surviving child.[15] The questionnaire consisted of 20 questions, the majority with "yes/no" responses, related to general health and utilization of specialized services related to movement, speech, hearing, behavior and education. The complete questionnaire is included in Appendix 1.

The **Ages and Stages Questionnaire (ASQ®-3)**, a validated developmental screening tool with approximately 40 "yes/no" or "yes/sometimes/not yet" questions designed to be completed by parents, was applicable to every child between the ages of 1 and 60 months. This evaluation tool has a high sensitivity and specificity to detect developmental delays in five domains: communication, gross-motor, fine-motor, problem-solving and personal-social.[16-18] After obtaining permission from the publishers, we integrated all 21 age-specific versions of the ASQ®-3 into REDCap as separate questionnaires.

The **Modified Checklist for Autism in Toddlers, Revised with Follow-up (M-CHAT-R/F)**, a validated autism screening tool with 20 “yes/no” questions designed to be completed by parents, was applicable to children between the ages of 16 and 30 months.[19, 20] With permission from the publishers, the M-CHAT-R/F was distributed as a REDCap questionnaire. Participants whose children had a positive M-CHAT-R/F screen received a phone call and completed a series of follow-up questions per screening protocol.

The ASQ®-3 and M-CHAT-R/F have been tested and validated in populations of children who are at risk for prematurity, autism and abnormal neurodevelopmental outcomes.[16-20] They were selected for this survey due to ease of completion and ease of distribution as REDCap questionnaires.

Finally, all surveys finished with a brief **Thank You Questionnaire (TYQ)** with 5 free-text and “yes/no” questions requesting permission to send a repeat survey 1 year later, the patient’s preferred method of contact for future studies, and a final request for permission to contact the patient to validate any results and/or obtain prior results from their child’s pediatrician’s office.

Distribution

The current age of all children surveyed was calculated, adjusting for prematurity until 24 months. For children who were older than 60 months, the CSQ, FCQ and TYQ were distributed at a single time-point. For children who were eligible for the ASQ®-3, the survey was automatically distributed on a rolling basis approximately 3 weeks prior to the date at which a child’s age-specific ASQ®-3 questionnaire would no longer be applicable. Depending upon the child’s age and the number of surviving children (determined via the CSQ), a parents’ survey queue (not including the single CSQ and TYQ) could contain as few as one FCQ questionnaire (e.g., one surviving child at 6 years of age) and as many as six questionnaires (e.g., two living children at 24 months of age).

Patients who did not respond to the initial survey invitation within one week received two additional weekly reminders via email, followed by a phone call.

Scoring and Questionnaire Reporting

Scripts in the R-programming language were used to automatically score completed ASQ®-3 questionnaires, accounting for an age-specific scoring rubric and adjustment for any skipped questions, and the M-CHAT-R/F. The ASQ®-3 was considered high-risk if any of the 5 domains assessed scored less than 2 standard deviations below the mean. The M-CHAT-R/F exam was considered high-risk if 3 or more questions had an atypical response. R-language scripting was also used to both identify any child who had a high-risk ASQ®-3 or M-CHAT-R/F screen, and to automate the creation of custom reports in Word using the *WordR*[21] and *officeR*[22] packages. These reports were distributed to parents via HIPAA secure email within 2 weeks of survey completion.

Repeat surveys

Patients who indicated they were amenable to a repeat survey received a second survey invitation in 2020 approximately 12-13 months after their 2019 response. All applicable age-specific questionnaires were repeated as part of a prospective analysis of pediatric developmental outcomes in this population. As part of the repeat 2020 survey, patients received a single email reminder but did not receive phone calls due to lack of available research staffing. Questionnaires and follow-up reports were generated and distributed automatedly within 2 weeks of survey completion.

Statistical Analysis

Power:

As a purely observational study, no official power analysis was performed, as the primary objective was to collect, to the fullest extent, parent-reported long-term outcomes in this population over a 2-year period.

Results

Figure 1 is a flow diagram of patient recruitment and responses. Four hundred and seventy-five patients underwent FLP for TTTS at our center between 09/23/2011 and 02/13/2019. Eighty-six patients were excluded from the study: 52 had no neonatal survivors, 32 did not have an email on file at the time of initial survey, and 2 did not consent to be contacted for future studies. A total of 389 mothers met inclusion criteria and received an invitation via email to participate in the 2019 survey. One hundred and forty-eight patients signed consent (38.0%), and 145 patients completed or partially completed the full survey (CSQ, FCQ, ASQ®-3, M-CHAT-R/F or TYQ) (37% response rate). One hundred and eight patients who responded in 2019 agreed to a repeat survey in 2020, of which 11 participants did not receive a repeat survey due to a technical error. In 2020, 97 patients from the 2019 cohort received a repeat survey, of whom 56 patients signed consent (57.8%) and 54 patients completed or partially completed the full set of questionnaires (55% response rate).

The majority of patients surveyed in 2019 and 2020 were from the southern United States (2019: 86.8% and 2020: 82.5%), had two neonatal survivors (2019: 83.5% and 2020: 84.5%) and underwent FLP for stage III TTTS (2019: 52.4%, 2020: 52.6%) (Table 1). Slightly more than half of patients each year were from Texas (2019: 55%, 2020: 52.5%), and relatively few delivered within the same hospital system as the FC (2019: 10.5%, 2020: 8.2%). Compared with non-responders, patients who consented to participate in the 2019 survey were older (30.0 vs 28.0 years, $p<0.001$) and had younger children at the time of survey (42.0 vs 52.0 months of age, $p = 0.005$), were less likely to have male children (47% vs 59%), had a higher incidence of co-existing twin-anemia polycythemia sequence (TAPS) (7.1% vs 5.1%, $p=0.016$), and had lower rates of co-existing selective fetal growth restriction (sFGR) (35% vs 47%, $p=0.026$) and donor twins weighed more at delivery (1360g vs 1570g, $p=0.028$). In both 2019 and 2020, there were no differences between responders and non-responders with respect to race, number of surveys to complete, incidence of triplet pregnancies, TTTS Quintero stage, cervical length, gestational age at FLP, gestational age at delivery, child survival status, region of origin, distance from the FC or incidence of delivery within the FC hospital system.

The completion rates and time to completion based on recorded survey timestamps in REDCap for each questionnaire are listed in Table 2. Reported completion times are limited to less than 60 minutes to exclude outliers who opened the questionnaire and completed it later. In 2019, 38% of eligible patients signed consent. 98% of consenting and eligible participants completed the CSQ, 87.8% completed the FCQ in a median [IQR] of 3 [2-5] minutes, 71.1% completed the ASQ®-3 in 4 [3-8] minutes and 86.4% completed the M-CHAT-R/F in 2 [1-3] minutes. Of the patients who signed consent, 110 (74.3%) completed the entire survey. Among patients who received a repeat survey in 2020, 57.8% of patients signed consent. 96.4% of consenting and eligible participants completed the CSQ, 91.1% completed the FCQ in 3 [2-5] minutes, 86.1% completed the ASQ®-3 in 6 [4-8.5]

minutes and 91.7% completed the M-CHAT-R/F in 2 [1-3]. Of the patients who signed consent, 45 (80.4%) completed the entire survey.

The rates of atypical developmental screens are listed in Table 3. When analysis of the ASQ®-3 was limited to the oldest assessment performed at ≥ 24 months of age for each child obtained in either 2019 or 2020, the overall rate of atypical ASQ®-3 was 18.9% (recipient twin: 19.6%, donor twin: 18.4%). In 2019 and 2020 the rate of atypical M-CHAT-R/F screens was 11.1% and 18.2%, respectively, for ex-recipient twins and 6.67% and 9.09%, respectively, for ex-donor twins. In 2019 and 2020, the follow-up M-CHAT-R/F telephone confirmation was not performed for 3 children (total 2 recipient and 1 donor) due to inability to reach the patient.

Patient willingness to undergo repeat survey and their preferred method of communication are listed in Table 4. Nearly 100% of patients in both years were amenable to a repeat survey in the following year. Respectively, most patients in 2019 and 2020 indicated a preference for email communication (90% vs 95.6%), followed by telephone calls (40% vs 37.8%), and finally mail-in post (21.8% vs 24.4%). In 2019 and 2020, 92.7% and 95.6% of responders were amenable to a follow-up call to sign release of information waivers to request medical records from their child's pediatrician's office.

Table 1. Baseline characteristics of survey participants stratified by response.

	2019			2020		
aracteristic	**No response** N = 244[a]	**Some response** N = 145[a]	**P-value**[b]	**No response** N = 43[a]	**Some response** N = 54[a]	**P-value**[b]
ernal age (years)	28.0 (23.0, 31.0)	30.0 (27.0, 35.0)	**<0.001**	30.0 (27.0, 33.5)	30.5 (27.0, 34.0)	0.5
iatric age (months, ected)[c]	52 (32, 72)	42 (17, 64)	**0.005**	55 (33, 86)	51 (32, 77)	0.4
e			0.13			0.3
African-American	29 (12%)	8 (5.5%)		2 (4.7%)	2 (3.7%)	
Asian	6 (2.5%)	4 (2.8%)		1 (2.3%)	0 (0%)	
Caucasian	150 (61%)	105 (72%)		30 (70%)	45 (83%)	
Hispanic	57 (23%)	27 (19%)		10 (23%)	7 (13%)	
Other	2 (0.8%)	1 (0.7%)				
stionnaire count[d]			0.11			0.6
3	12 (4.9%)	5 (3.4%)		3 (7.0%)	3 (5.6%)	
4	92 (38%)	37 (26%)		17 (40%)	20 (37%)	
5	9 (3.7%)	5 (3.4%)		2 (4.7%)	0 (0%)	
6	110 (45%)	81 (56%)		15 (35%)	19 (35%)	
8	21 (8.6%)	17 (12%)		6 (14%)	12 (22%)	
der: male	143 (59%)	68 (47%)	**0.025**	19 (44%)	30 (56%)	0.3
n type			0.2			0.6
MCDA	234 (96%)	138 (95%)		42 (98%)	50 (93%)	
MCMA	0 (0%)	2 (1.4%)		0 (0%)	2 (3.7%)	
Higher order	10 (4.1%)[e]	5 (3.4%)		1 (2.3%)	2 (3.7%)	

lets	9 (3.7%)	5 (3.4%)	>0.9	1 (2.3%)	2 (3.7%)	>0.9
let type			>0.9			0.3
DCTA	8 (89%)	4 (80%)		0 (0%)	2 (100%)	
MCTA	1 (11%)	1 (20%)		1 (100%)	0 (0%)	
TS Quintero stage			0.7			>0.9
I	33 (14%)	17 (12%)		3 (7.0%)	7 (13%)	
II	64 (26%)	45 (31%)		14 (33%)	16 (30%)	
III	133 (55%)	72 (50%)		24 (56%)	28 (52%)	
IV	9 (3.7%)	7 (4.8%)		2 (4.7%)	2 (3.7%)	
Isolated TAPS[f]	5 (2.0%)	4 (2.8%)		0 (0%)	1 (1.9%)	
TS + TAPS[f]	5 (2.1%)	10 (7.1%)	**0.016**	3 (7.0%)	2 (3.8%)	0.7
TS + sFGR[g]	114 (47%)	51 (35%)	**0.026**	18 (42%)	20 (37%)	0.6
rocedure						
FLS (percutaneous)	226 (93%)	138 (95%)	0.3	42 (98%)	50 (93%)	0.6
FLS (laparoscopic-assisted)	16 (6.6%)	5 (3.4%)		1 (2.3%)	2 (3.7%)	
Selective reduction	1 (0.4%)[h]	2 (1.4%)[i]		0 (0%)	2 (3.7%)[i]	
Failed laser, amnioreduction ONLY	1 (0.4%)[j]	0 (0%)				
uired repeat procedure	2 (0.8%)[k]	3 (2.1%)[l]	0.4	2 (4.7%)[m]	1 (1.9%)[n]	0.6
rtwin weight ordance (%)[o]	25 (16, 34)	22 (13, 30)	**0.024**	21 (16, 32)	22 (14, 31)	0.8
vical length (mm)	38 (31, 45)	40 (32, 47)	0.3	42 (33, 47)	39 (29, 48)	0.4
. at FLS (weeks)	20.43 (18.82, 22.29)	20.43 (18.71, 22.29)	0.8	20.29 (18.36, 22.14)	20.14 (18.75, 22.25)	>0.9
. at delivery (weeks)	32.0 (29.4, 34.1)	32.3 (29.4, 34.3)	0.5	32.86 (31.00, 34.57)	32.00 (29.46, 34.68)	0.2
ipient birthweight (g)	1,725 (1,283, 2,139)	1,778 (1,391, 2,193)	0.2	1,860 (1,625, 2,248)	1,830 (1,326, 2,171)	0.4
nor birthweight (g)	1,360 (975, 1,890)	1,570 (1,170, 2,000)	**0.028**	1,730 (1,300, 2,094)	1,570 (1,170, 2,020)	0.6
ld status			0.2			0.2
Ex-donor loss	40 (16%)	14 (9.7%)		7 (16%)	5 (9.3%)	
Dual survivors	198 (81%)	127 (88%)		36 (84%)	46 (85%)	
Ex-recipient loss	6 (2.5%)	4 (2.8%)		0 (0%)	3 (5.6%)	
ion of origin			0.12			0.4
Midwest	21 (8.7%)	9 (6.2%)		2 (4.7%)	5 (9.3%)	
South	212 (88%)	124 (86%)		38 (88%)	42 (78%)	
West	9 (3.7%)	12 (8.3%)		3 (7.0%)	7 (13%)	
as based	134 (55%)	81 (56%)	0.9	24 (56%)	27 (50%)	0.6
ance from FC (miles)	266 (189, 454)	237 (150, 489)	0.12	237 (151, 590)	232 (169, 637)	0.7
ivered within FC pital system	24 (9.8%)	17 (12%)	0.6	5 (12%)	3 (5.6%)	0.5

., gestational age; MCDA, monochorionic diamniotic; MCMA, monochorionic monoamniotic; DCTA, dichorionic triamniotic; TA, monochorionic triamniotic; TTTS, twin-twin transfusion syndrome; TAPS, twin anemia polycythemia sequence; FLS, scopic laser surgery; FI, fetal intervention; sFGR, selective fetal growth restriction; FC, fetal center

Median (IQR); n (%)

lcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test

diatric age corrected for prematurity until 24 months of age

mber of questionnaires to be performed based on child's age at time of survey. Does not include CSQ and TYQ.

triplet gestations with exception of a single quadruplet (dichorionic quadramniotic, non-respondent)

fined as delta MCA-PSV ≥ 1

fined as ≥ 25% inter-twin estimated weigh discordance and either donor or recipient twin estimated fetal weight < 10%ile at FI

CDA pregnancy in which cords too close for FLS, bipolar cord coagulation performed

DMO with TTTS converted to bipolar after FLS (N = 1); TTTS with sFGR, primary radiofrequency ablation of donor twin (N = 1)
intero Stage II with poor visualization on diagnostic fetoscopy secondary to prior bleed, amnioreduction only performed (N = 1)
intero Stage II FLS at 18w0d, followed by recurrent TTTS/TAPS and ventriculomegaly in donor at 19w6d and underwent RFA (N
); Quintero Stage II FLS for DCTA triplet gestation at 18w3d with RFA of donor due to recurrent TTTS/TAPS at 20w1d(N = 1)
intero Stage III TTTS FLS at 21w2d with recurrent TTTS at 24w5d and underwent repeat FLS (N = 1); Quintero Stage IV at
v3d with recurrent TTTS at 24w0d underwent repeat FLS (N= 1); Quintero Stage II TTTS FLS at 18w2d with recurrent TAPS and
niotic band at 20w0d had repeat FLS and amniotic band lysis from neck of plethoric fetus (N = 1)
uintero Stage III TTTS at 21w2d with recurrent Stage III TTTS underwent repeat FLS at 24w5d (N = 1); Quintero Stage II TTTS
S at 18w2d with recurrent TAPS and amniotic band at 20w0d had repeat FLS and amniotic band lysis from neck of plethoric fetus
= 1)
intero Stage IV FLS at 16w3d with recurrent TTTS and repeat FLS at 24w0d
efined as inter-twin estimated fetal weight discordance of ≥ 25% and either the donor or recipient estimated fetal weight < 10%
ck)

Table 2. Survey Response rate[a] among patients who had FLS between 09/23/2011 and 02/13/2019

	Eligible	Completed	Completion time (min)[b]	Response Rate
Questionnaire (2019 Survey)				
Consent	389	148	-	38.0%
CSQ	148[g]	145	-	98%
FCQ[c]	148[g]	130[e]	3 (2, 5)	87.8%
ASQ®-3[d]	100[g]	81[e]	5 (3, 8)	71.1%
M-CHAT-R/F[e]	22[g]	19	2 (1, 3)	86.4%
TYQ	148[g]	110	-	74.3%[h]
Questionnaire (2020 Survey)				
Consent	97	56	-	57.8%
CSQ	56[g]	54	-	96.4%
FCQ[c]	56[g]	51[f]	3 (2, 5)	91.1%
ASQ®-3[d]	36[g]	31	6 (4, 8.5)	86.1%
M-CHAT-R/F[e]	12[g]	11	2 (1, 3)	91.7%
TYQ	56[g]	45	-	80.4%[h]

CSQ, child status questionnaire; FCQ, fetal center questionnaire, ASQ®-3, ages and stages questionnaire, M-CHAT-R/F, modified checklist for autism in toddlers

[a]Counts represent number of patients surveyed

[b]Median (IQR), excluding outliers > 60minutes; time to complete the Consent, CSQ and TYQ was not recorded

[c]All mothers eligible

[d]Patients with children between ages 1-60 months eligible
Patients with children between ages of 16-30 months eligible

[e]Does not include 1 partial response

[f]Does not include 2 partial response

[g]Represents the number of patients who signed consent and eligible for survey

[h]Represents the percentage of patients who signed consent who finished the entire survey

Table 3. Atypical developmental screens in 2019 and 2020 by twin

	Twin		Total
	Ex-Recipient	Ex-Donor	
ASQ®-3 Questionnaire (2019 + 2020 Survey) ≥ 24mo age			
Typical	37 (80.4%)	40 (81.6%)	77 (80.2%)
Atypical[a]	9 (19.6%)	9 (18.4%)	18 (18.9%)
M-CHAT-R/F Questionnaire (2019 Survey)			
Typical	16 (88.9%)	14 (93.3%)	30 (90.9%)
Atypical[b]	2 (11.1%)[c]	1 (6.67%)	3 (9.1%)
M-CHAT-R/F Questionnaire (2020 Survey)			
Typical	9 (81.8%)	10 (90.9%)	19 (86.4%)
Atypical[b]	2 (18.2%)[d]	1 (9.09%)[d]	3 (13.6%)

[a]Indicates at least one domain on the ASQ®-3 for which the score was < 2 SD below the mean.
[b]Indicates 3 or more atypical responses
[c]Unable to contact a single patient to confirm atypical response
[d]Unable to contact a single patient (flagged recipient and donor) to confirm atypical response

Table 4. Results of thank you questionnaire (TYQ)

Survey year	**Ok to contact for repeat survey?**	**Preferred method of future contact**			**Ok to inquire about pediatrician records?**
		Telephone	**Email**	**Post[a]**	
2019	109 (99.1%)	44 (40%)	99 (90%)	24 (21.8%)	102 (92.7%)
2020	45 (100%)	17 (37.8%)	43 (95.6%)	11 (24.4%)	43 (95.6%)

[a]2 patients who requested communication via post and provided their current home address had moved 115 miles and 1577 miles since time of initial evaluation for FLP

Discussion

Principal Findings

In this survey study, we effectively gathered long-term pediatric parent-reported outcomes in patients treated with FLP for TTTS via email and electronic questionnaires. The overall response rates to our survey were 37.3% in 2019 and 55.7% in 2020. Notably, slightly less than half of the patients who responded were from outside of Texas (44% in 2019 and 50% in 2020), and the majority (88% in 2019 and 94.4% in 2020) delivered outside the FC hospital system. Of the patients who consented for our survey, the overall completion rate was 74.3% in 2019 and 80.4% in 2020.

Comparison with prior work

Compared with patients in Europe, the long-term pediatric outcomes in patients who travel for the treatment of TTTS in the United States have been poorly studied. Several Western European centers in which a centralized healthcare systems exist have reported on in-person evaluation of large cohorts of pediatric survivors of TTTS with near 100% follow-up rates.[8, 23-24] Conversely, there is but a single report of long-term outcomes in children assessed solely in the United States.[25] In that study, only 13% of patients from outside the study center state were available for in-person assessment. This lack of data on long-term outcomes represents a critically missing component with which to counsel patients who are evaluated and treated for TTTS in the United States.

There are several challenges which contribute to the difficulty in assessing long-term pediatric outcomes in patients treated for TTTS in the United States. First, the geographic distance patients travel for specialized fetal intervention care is a physical barrier to in-person follow-up.[13] As a niche specialty, few high-volume academic centers account for the majority of FLP procedures performed annually.[26] Consequently, patients who reside outside these locations will travel great distances to receive care during their pregnancy, only to return home for follow-up care. This is evidenced by the geographic distance from our center in the population of patients surveyed, and the high proportion of patients who delivered outside the FC hospital system.

Second, compared with other high-income countries, the United States ranks last regarding measures of health care affordability and access to care.[27] As of 2023. approximately 25.3 million people were uninsured in the U.S.[28] Furthermore, as of 2016, there were 626 individual health systems identified across the United States.[29] Both the lack of access to care and the complex system of health care networks may contribute to the challenges in longitudinal assessment of pediatric patients.

Finally, in most health systems in the United States, a fetus is not assigned a medical record number despite being exposed to disease, medications and even fetal surgical interventions prior to birth. Both technical and legal challenges have likely contributed to the barriers surrounding the creation of a fetal electronic health record. Historically, fetal data are linked to pediatric outcomes via the maternal chart, so any attempt to fully describe an individual's medical history, from the time of conception to pediatric and adult life, requires the additional step of linking these two individuals. Despite some recent strategies to create nested or embedded fetal records within a maternal record,[30] this has not been universally adopted in the field of obstetrics and fetal surgery.

Considering the challenges in obtaining long-term pediatric outcomes in patients treated for TTTS, validated parent-reported screening questionnaires delivered via electronic media are a potential starting point towards addressing this problem. We acknowledge that the gold standard for pediatric neurodevelopmental evaluation is in-person assessment. However, in the context of a population of individuals spread across a large geographic area and amongst various healthcare networks with diverse levels of access to care, remote screening provides a unique opportunity to assess outcomes in this population.

The use of electronic patient-reported outcome (ePROM) tools has increased with the growth of electronic health technologies. Significant advantages of this strategy include the ability to obtain information remotely over great distances and doing so at relatively low cost with the help of computer programming and automation. Furthermore, the real-time analysis of patient-reported data allows for early detection of positive screens and improvements in patient-clinician communication.[31] In our study, we developed scripts to automatically generate both accurate and personalized reports for children who had positive screens, which were subsequently returned to participants to share with their primary physician, thereby illustrating the potential clinical utility of this tool.

Strengths and Limitations

To our knowledge, this is the first report in fetal medicine of the ASQ®-3 and M-CHAT-R/F being delivered to study participants via REDCap questionnaire. Previous studies of TTTS survivors describe distribution of the ASQ®-3 to patients via post,[32-35] email attachment[32] or telephone interview,[32] but incorporating these surveys into a digital format for research in fetal medicine has not been previously reported. This novel approach allowed for the application of computer-based algorithms to schedule timely distribution of surveys, automate questionnaire scoring, and generate individualized reports for atypical screening responses. Furthermore, the costs to implement this system within an academic university hospital system where REDCap is an established research tool were minimal and involved licensing of the ASQ®-3 for distribution as a research questionnaire. Unlike in-person assessments, which require significant human capital, the entire project was developed and executed by a few individuals with a background in both medicine and computer programming. Using this system, we received a partial or full response from patients in 20 different states at an average of 355 miles (min: 5.61, max: 1629) from our center. Furthermore, among patients who consented to the study, the questionnaire completion rate was very high, suggesting that collection of long-term parent-reported outcomes via electronic format is technically feasible, and that the questionnaires chosen for the study were not overly burdensome to complete. Finally, among participants who completed the study, there was a strong willingness to repeat a future assessment and a high rate of participation in the second year.

Regarding limitations, it is important to remember that the results from this study represent screening exams and cannot necessarily be used to diagnose atypical pediatric development. As the data are parent-reported, there is a possible bias toward either under-reporting or over-estimating a child's capabilities.[21] Furthermore, when compared to non-responders, the inter-twin fetal growth discordance, a marker of placental insufficiency and risk factor for increased neonatal morbidity/mortality, was lower in the patients who responded to the survey, which may bias the results towards a healthier population of individuals. Although most patients indicated they would

consider providing pediatric records for evaluation, the study resources did not let us validate the questionnaires. It is, however, reassuring that the rates of atypical ASQ®-3 screens ASQ in our cohort are comparable with rates of neurodevelopmental impairment, as assessed via Bayley Scales of Infant Development BSID, which is administered in person, in several large European cohorts of patients treated for TTTS.[8, 23-24]

This was also a retrospective study, and patients were approached via email. It is possible that over time, patients' contact information and email addresses changed, which may explain why non-responders tended to have older children. A future study in which patients are enrolled prospectively and receive an in-person explanation of the study procedures and study purpose may lead to improved initial response rates.

Unfortunately, 32 patients were not eligible for the study due to not having an email on file. These patients, in addition to the non-responders, may be less technically savvy and could represent a digital divide bias that favors participants who are more computer-literate or can afford a computer. Potentially offering the survey via telephone, via post or via alternative electronic media such as text-messaging may have improved response rates. In addition, the response rate may have been improved if participation had been incentivized, as participation was entirely voluntary.

The project was also only available in English. Without a field to indicate the patient's preferred language, it is possible some patients for whom English was not their primarily language received the study, although it is unlikely that they would have completed the questionnaires. Additional limitations include a lack of information regarding patient insurance status which may be an important contributor to neurodevelopmental outcomes and the absence of a control group for comparison. Finally, 11 patients who agreed to repeat survey did not receive a repeat survey invitation in 2020 due to a technical coding error which was not identified until after study completion. Furthermore, we were unable to reach several patients to confirm the results of atypical M-CHAT-R/F screens.

Conclusions

In conclusion, this study represents the largest cohort of long-term outcomes reported in a population of patients treated with FLS for TTTS in the United States. The novel use of computer programming and REDCap allowed us to automate the distribution, scoring, and generation of custom reports with ease and at relatively low cost. Future longitudinal studies in this population may benefit from prospective enrollment, incentivized participation, and survey distribution via alternative electronic methods such as text-messaging.

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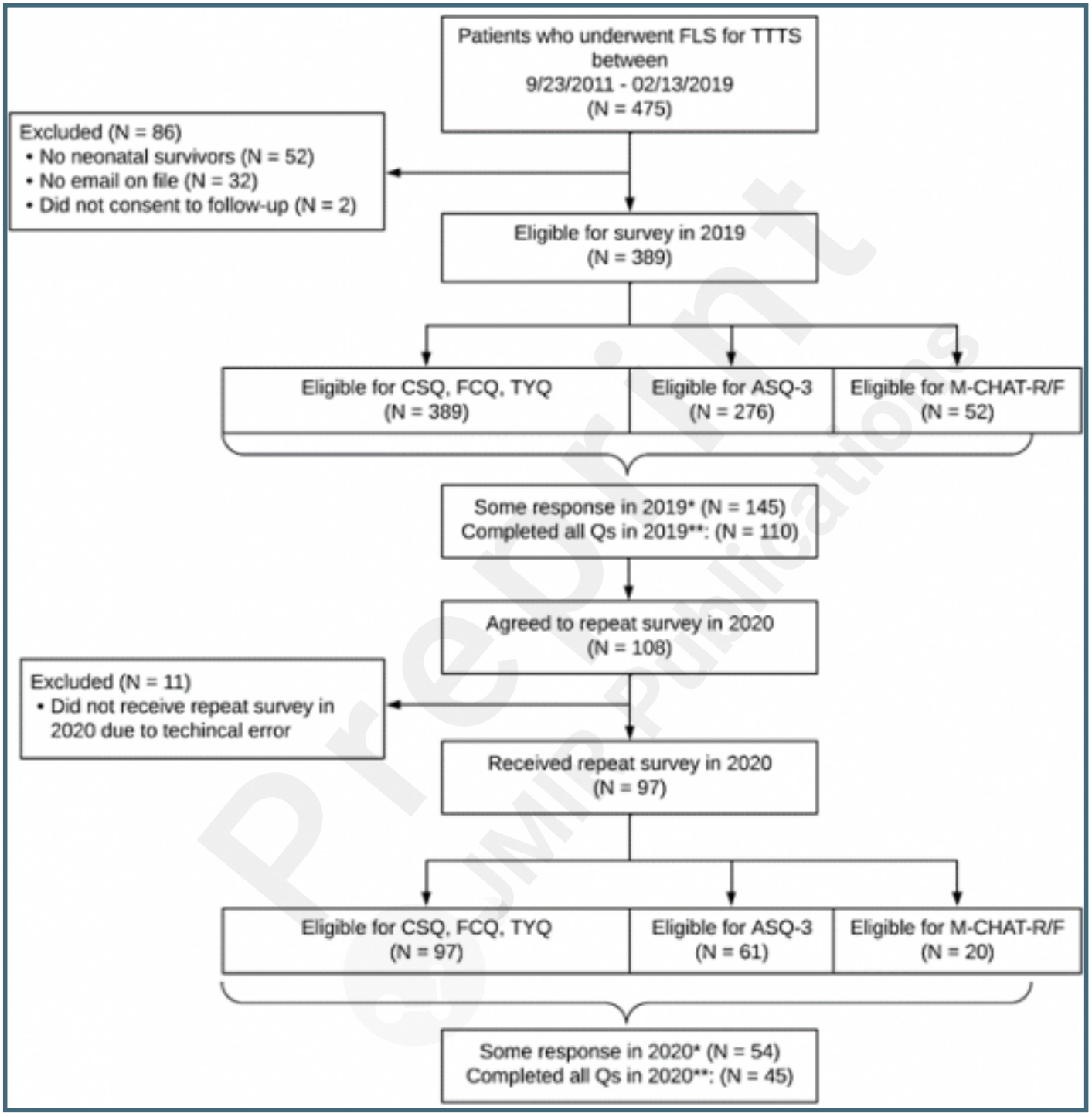
Supplementary Files

Figures

Patient recruitment and responses. *Some response to any of CSQ, FCQ, ASQ, or M-CHAT-R/F. **Completed all age-appropriate questionnaires (Qs).



Multimedia Appendixes

Fetal Center Questionnaire.
URL: http://asset.jmir.pub/assets/5067968a11eafbfbef9cb1c5a0986023.docx