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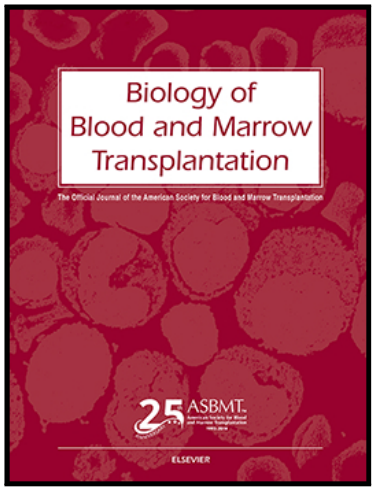

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Highlights

- Stem cell transplant can retard the progression of early infantile Krabbe disease
- Superior functional outcomes are achieved if performed before 30 days of life
- Accelerated timeline for diagnosis, evaluation, and intervention must be followed

Long-Term Functional Outcomes following Hematopoietic Stem Cell Transplant for Early Infantile Krabbe Disease

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Short Title: Long-term Post-Transplant Outcomes for Krabbe Disease

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation (HSCT) can retard the progression of early infantile Krabbe disease (EIKD). Superior outcomes are achieved if HSCT is performed prior to the onset of symptoms, however little information is available about the long-term outcomes in surviving patients. We now describe functional outcomes in pre-symptomatic infants who underwent HSCT for EIKD at ≤2 months of life. Records of the 19 patients who underwent HSCT for EIKD at ≤2 months of age from 1996-2010 were reviewed. Long-term functional outcomes were compared between those transplanted at <30 days and ≥30 days of life. Median age at transplant was 27 days (range 19-61). Median follow-up of the cohort was 12.6 years. Overall survival at 5 and 10 years post-transplant was 84.2% (95% CI:58.7-94.6%) and 78.6% (95% CI:52.5-91.4%), respectively. More favorable outcomes were seen in patients who underwent HSCT at <30 days of age, particularly in domains of mobility (p=0.01), communication (p=0.02), and feeding (p=0.008). Improved functional outcomes were observed when HSCT was performed in the first month of life, defining a critical period for intervention. These results support the implementation of newborn screening to enable rapid diagnosis and early treatment of infants with EIKD.

KEYWORDS: umbilical cord blood transplantation, Krabbe disease

INTRODUCTION

Krabbe disease, also known as globoid leukodystrophy, is a progressive and fatal neurologic disease caused by autosomal recessive mutations in the galactocerebrosidase (GALC) gene, which lead to deficiency of the enzyme galactocerebrosidase. As a result, psychosine and other toxic metabolites accumulate and severe demyelination occurs.[1] In the most severe form, early infantile Krabbe disease (EIKD), patients develop severe irritability, poor feeding and spasticity in the first months of life with subsequent neurodegeneration and death by 2 years of age if untreated. EIKD is a very rare disease, estimated to occur at a frequency of 1 in 400,000-500,000 live births. Allogeneic hematopoietic stem cell transplantation (HSCT) can retard disease progression and extend life through engraftment of donor-derived, enzyme-producing cells in the bone marrow, brain and other organs.[2-13] Previous studies have shown that patients transplanted after development of clinical symptoms have poor functional outcomes and low rates of survival. In contrast, clinical outcomes are favorable if HSCT is performed prior to the onset of symptoms.[9,13] Due to the severe and rapidly progressive nature of EIKD, most affected patients who are able to undergo HSCT early enough for potential benefit are diagnosed early either because of a family history of the disease or through newborn screening. Cord blood units are frequently utilized as the allogeneic donor source for patients with EIKD because of their rapid availability for urgent transplantation.

While HSCT in patients with Krabbe disease extends life, there is little information available regarding the long-term function and quality of life for surviving patients. Because HSCT is associated with significant risks of early mortality and late morbidity, information about long-term outcomes is necessary to inform parental decisions about early intervention with HSCT, long-term care for individuals, and policies for newborn screening. Our center has focused on the

treatment of patients with EIKD with HSCT for over 2 decades. We now report the results of a retrospective review of patients with EIKD who underwent HSCT at ≤ 2 months of age, describing the long-term functional outcomes observed in the cohort at 5 years post-HSCT and beyond. We hypothesized that younger age at transplant would result in improved functional outcomes in this patient cohort.

MATERIALS AND METHODS

Study Design

The study was designed as a single-center, retrospective review of clinical data routinely collected by the Pediatric Blood and Marrow Transplant Program at Duke University Medical Center (DUMC). Patients were selected from a cohort of patients with early infantile Krabbe disease, who underwent HSCT at 2 months of age or younger from December 1996 to July 2010, to allow for a minimum of 5 years of follow-up post-transplantation. Two patients underwent HSCT at outside institutions but were followed post-HSCT at DUMC. All patients who underwent HSCT at DUMC were enrolled in an Institutional Review Board-approved protocol or treatment plan for transplant and written informed consent was obtained from the parents or legal guardians of all patients prior to the initiation of conditioning therapy. Institutional Review Board approval was also obtained for this retrospective review.

Eligibility

Eligibility criteria included a confirmed diagnosis of early infantile Krabbe disease, known pathogenic mutation(s), abnormal neurophysiologic testing and neuroimaging, age ≤ 2 months, and transplant date prior to September 2010. The details of transplantation, including myeloablative chemotherapy for conditioning, engraftment, transplant-related complications,

graft versus host disease and overall survival for a subset of the patients were previously reported.[7,10,13]

Data Collection

Patients were evaluated pre-transplant with a battery of neurophysiological, neurofunctional and neuroimaging tests and routinely evaluated for follow-up transplant care at Duke at a minimum of every 3-6 months for the first year, every 6 months for the second year, and then minimally on an annual basis. Duke medical records were reviewed to collate data from these follow-up visits, including physical examinations and assessments of disease status, growth and organ function were performed. Performance status by Lansky scale, was not analyzed in this report. The functional outcomes of mobility, communication, and feeding were pre-specified as primary outcomes because they are meaningful indicators of relevant adaptive skills. Mobility outcomes were divided into 3 categories: walking without assistance, walking but requiring assistive device such as a walker, and wheelchair bound. Expressive communication was categorized as verbal with normal speech pattern, verbal with abnormal speech pattern, nonverbal but able to communicate with an assistive device/method, or noncommunicative. Feeding abilities were characterized as follows: feeds solely and independently by mouth, feeds solely by mouth but requires assistance, requires a tube but able to do some feeding by mouth, and feeds solely via tube. Secondary outcomes included school attendance (appropriate grade level for age, below grade level for age, or not attending), school performance (attending mainstream classes without specialized resources, requiring specialized resources, or not attending), and presence or absence of spasticity, seizures, hearing loss, vision loss, dental problems, aspiration events, and bowel/bladder incontinence. All outcomes were assessed at 5 years post-HSCT and at the most-recent follow-up visit.

Statistical Analysis

Descriptive statistics are presented for baseline characteristics and functional outcomes at 5 years post-transplant and the most recent follow-up. Fisher's Exact test was used to compare outcomes between groups at both time points. The Kaplan-Meier method was used to estimate survival at 5 and 10 years post-transplant in the entire cohort and separately by timing of transplant (< 30 days vs. ≥ 30 days of life). Analyses were conducted using SAS version 9.4 Cary, NC) and R version 3.2.3.

RESULTS

Patient Characteristics

Nineteen patients underwent HSCT for infantile Krabbe disease from October 1996-May 2010. Patient, donor, and transplant characteristics of the study cohort are shown in Table 1. The median age at transplant was 27 days (range 19-61) with 12 and 7 patients undergoing transplantation at < 30 and ≥ 30 days of age, respectively. Five patients were intentionally delivered prematurely, between gestational ages of 35-37 weeks, after demonstration of fetal lung maturity, to enable transplant as early in life as possible. The remaining 14 patients were born at term. The majority of patients were diagnosed due to family history (84.2%) and the remainder (n = 3, 15.8%) were diagnosed via newborn screening in New York state.[11-12] All babies had a confirmed diagnosis of EIKD with documentation of the presence of pathological mutations as well as multiple abnormalities in neurological tests prior to transplantation as described previously by Krivit, et al and Escolar, et al.[6,13]

Transplant Characteristics

All but one patient received umbilical cord blood units (CBU) from unrelated donors. One patient, the first transplanted at our center over 20 years ago, received bone marrow from a carrier, human leukocyte antigen (HLA)-matched, fraternal twin. The majority of patients received cord blood units matched at 4/6 (53%) or 5/6 (42%) by low and intermediate resolution class I (HLA-A and –B) and high resolution class II (HLA-DRB1) typing. The cord blood cell doses were high because of the small size of the patients at transplant. Conditioning regimens did not include total body irradiation (TBI) due to patient age and diagnosis. All 18 patients who underwent unrelated umbilical cord blood transplantation (UCBT) received 9 days of myeloablative chemotherapy with busulfan, adjusted based on pharmacokinetic data, cyclophosphamide, and anti-thymocyte globulin.[10] Three patients developed chronic graft versus host disease (cGvHD); only one patient has cGvHD at most recent follow-up with limited intermittent skin involvement requiring only topical therapy. The one patient who underwent bone marrow transplantation from a matched related donor (MRD-BMT) received busulfan and cyclophosphamide without ATG. All patients who survived to 5 years post-transplant were durably engrafted with donor cells and had normal galactocerebrosidase levels. All UCBT recipients had full donor chimerism. The patient who underwent MRD-BMT at > 30 days old maintained stable mixed (70-80% donor) chimerism from whole blood for over 2 decades.

Survival

Overall survival was 84.2% (95% CI 58.7-94.6) at 5 years post-transplant and 78.6% at 10 years post-transplant for all patients (95% CI 52.5-91.4, Figure 1). There was no statistically significant difference in overall survival between the < 30 and ≥ 30 days of age at transplant

groups at 5 years (p = 0.95) or at 10 years (p = 0.65). There were 3 deaths prior to 5 years post-transplant, all of which were transplant-related and occurred 1-2 months post-transplant. There were 2 deaths after 5 years post-transplant. One patient, who underwent UCBT at 36 days of life, died due to disease progression 15.5 years post-transplant. At 5 years post-transplant, she was wheelchair bound, was fed by mouth, communicated via assistive device, and attended regular, mainstream classes at an age-appropriate grade level. At last follow-up prior to her death, she was fed by mouth with supplemental feeds via G-tube and continued to attend regular, mainstream classes at an age-appropriate grade level. Another patient, who underwent UCBT at 21 days of life, developed an idiopathic and fatal reaction to ketamine following surgical tendon release 6.3 years post-transplant. Three of the 5 deaths occurred among patients transplanted at < 30 days of age.

Primary Functional Outcomes

Functional outcomes were assessed in all 16 surviving patients at 5 years and at most recent follow-up which occurred at a median of 12.6 years (range 5.2-18.8); the distribution of this timing is shown in Figure S1. There was no statistically significant difference in follow-up time between those who underwent HSCT at < 30 days (median 12.1 years, range 6.3-16.4) and ≥ 30 days of life (median 14.7 years, range 5.6-19.1, p = 0.42, Wilcoxon rank sum test).

Mobility: Mobility was superior in those babies who underwent HSCT at < 30 days (p = 0.02 at 5 years, p = 0.01 at most recent follow-up). At both 5 years post-transplant and the most recent follow-up, 90% of those who underwent HSCT at < 30 days were walking, either independently or with assistive devices. Only 1 (10%) of the infants transplanted at < 30 days was wheelchair bound, whereas only 1 (16.7) of the infants transplanted at ≥ 30 days was not confined to a wheelchair (Table 2, Figure 2 a-b).

Communication: Expressive communication was significantly better in those babies < 30 days old at HSCT at both 5 years post-HSCT and most recent follow-up (p = 0.02, Table 2, Figure 2 c-d). All 10 patients who underwent HSCT at < 30 days were verbal, and 80% had normal speech. Half of the patients who underwent HSCT at ≥ 30 days were verbal, 2 (33.3%) required assistive communication device, and 1 was non-communicative. Communicative abilities were stable between the 2 evaluation time points.

Feeding: Feeding outcomes were not significantly different between groups at 5 years post-transplant. However, differences were seen at the most recent follow-up. At that time point, feeding outcomes were better in those who underwent HSCT at < 30 days (p = 0.008). All but 1 patient (90%) transplanted at < 30 days fed by mouth independently. In those who underwent HSCT at ≥ 30 days, only 1 patient (16.7%) fed by mouth independently and the remainder received enteral nutrition via G-tube (Table 2, Figure 2 e-f).

Secondary Functional Outcomes

All patients had normal vision and hearing. At both 5 years post-HSCT and most recent follow-up, 68.8% of the cohort was attending school at an age-appropriate grade level. At most recent follow-up, 56% required some support with specialized resources and 1 patient was unable to attend school. Abnormal dentition was observed in all patients surviving beyond 5 years post-HSCT (Table 3). The majority of patients (87.5%) had generalized spasticity at both 5 years post-HSCT and at most recent follow-up. Two patients (12.5%), both of whom were ≥ 30 days old at HSCT, had ongoing seizures. Two patients had aspiration events and bowel/bladder incontinence at both 5 years and most recent follow-up; both underwent HSCT at ≥ 30 days of

life. None of the secondary outcomes were statistically significantly different in children transplanted < or ≥ 30 days of age.

DISCUSSION

This is the first report of late outcomes of early transplantation in infants with EIKD. Our results demonstrate that survival in infants transplanted for EIKD before 2 months of age is extended beyond what is expected without treatment, and functional outcomes are more favorable when infants are transplanted before the first month of life. These results highlight the need for an accelerated timeline for diagnosis, evaluation and decision-making regarding HSCT. Of note, 2 of the 3 patients diagnosed via NBS underwent transplant at > 30 days post-transplant (32 and 40 days), due to complicating social/socioeconomic factors. States implementing NBS for EIKD must develop efficient systems to rapidly confirm diagnosis, educated parents and facilitate referrals to transplant centers to ensure timely workup and initiation of chemotherapy by 2 weeks of age to enable transplant before 30 days of age. This is an ambitious goal but can be achieved with prior planning, established relationships and streamlined communications.

Currently HSCT is the only available therapy for EIKD. Even when performed at ≦ 2 months of age, most long-term survivors of HSCT for EIKD had some degree of functional impairment. As such, patients who have undergone HSCT for EIKD require comprehensive long-term follow-up. In addition to standard post-transplantation evaluations, annual studies should include magnetic resonance imaging, electroencephalogram, electromyogram/nerve conduction studies, brainstem auditory evoked response, visual evoked potentials and galactocerebrosidase level. Developmental and neurocognitive evaluation should be performed at least annually and school performance should be followed closely. Information obtained should be used to guide additional

therapies (i.e. physical, occupational, and speech therapies), resources, and learning/testing accommodations. In addition, dental examination should be performed every 6 months. Abnormal dentition was present in all patients who survived to at least 5 years post-HSCT, an effect that is uniquely associated with the use of chemotherapy in the very young child.[14-16]

We previously reported late effects after HSCT in children < 2 years of age using busulfan-based, myeloablative conditioning.[16] The outcomes in the current study cannot be compared directly with those in the prior report; all of the patients who underwent HSCT at < 2 months in the prior study did so for EIKD and are included in the current report. There were however, 10 patients who underwent HSCT at ≤ 6 months of age for nonmetabolic diseases which serve as a comparison group. None of these previously reported patients required assistance with walking or were wheelchair bound. All communicated verbally and only one had abnormal speech. All attended school in age-appropriate grade levels and 3 (30%) require special resources including individualized education plans or special education. None have generalized spasticity, seizures, scoliosis, or incontinence. These data strongly support the conclusion that the long-term functional outcomes observed in the current cohort are associated with the underlying metabolic disorder and not the chemotherapy or other drugs used during transplantation as they were not observed in those patients who underwent HSCT at young ages for other nonmetabolic diagnoses.

While improved outcomes for infants with EIKD were observed when transplant was performed prior to 30 days of life, further improvement is needed. The majority of children, while considerably improved compared to the natural history of this disease, continue to have functional impairments. In this cohort, only 2 of 12 children transplanted before 30 days of age, had normal function in terms of the primary and secondary outcomes analyzed in this report.

New strategies to supplement transplantation are needed to normalize the lives of children with EIKD. Examples of such strategies currently under investigation include gene therapy, fetal umbilical cord blood transplantation, and augmentation of standard UCBT with intrathecally delivered cellular therapies after bone marrow engraftment.[17] This is the first report of long-term functional outcomes following HSCT for EIKD. The major limitation of this study was the small sample size, which is due to the rarity of the disease and the paucity of patients diagnosed and transplanted in the first few months of life. Nonetheless, our study has clearly demonstrated the benefits of performing HSCT within the first month of life. These results should help inform clinical care, policy regarding screening, and decision-making with individual families.

In summary, patients with early infantile Krabbe disease who are transplanted at < 30 days of life have more favorable outcomes in communication, feeding, and mobility than those transplanted between 30-61 days of age. Early diagnosis and intervention are critical for improving long-term functional outcomes. For pre-symptomatic newborns diagnosed with Krabbe, an accelerated timeline must be followed for evaluation and decision-making regarding HSCT.

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TABLES

Table 1. Patient, Donor/Transplant Characteristics

Patient Characteristics		**Median (range)**
Age at transplant (days)		27 (19-61)
Time from transplant at analysis (years)		11.2 (0.1-18.8)
Gestation age at birth:		**N (%)**
	35-37 weeks	5 (26.3)
	> 37 weeks	14 (73.7)
Diagnosis:	Family history	16 (84.2)
	Newborn screening	3 (15.8)
Gender:	Male	8 (42.1)
Race:	Caucasian	16 (84.2)
Ethnicity:	Hispanic	3 (15.8)
Donor/Transplant Characteristics		**N (%)**
Graft source:	UCBT	18 (94.7)
	MRD-BMT	1 (5.3)
HLA Matching:	6/6	1 (5.3)
	5/6	8 (42.1)
	4/6	10 (52.6)
Conditioning regimen:	Bu/Cy/ATG	18 (94.7)
	Bu/Cy	1 (5.3)*

* Patient underwent MRD-BMT; UCBT = unrelated umbilical cord blood transplantation, MRD-BMT = matched related donor bone marrow transplantation, HLA = human leukocyte antigen, Bu = busulfan, Cy = cyclophosphamide, ATG = anti-thymocyte globulin

Table 2. Primary Functional Outcomes

Outcomes at 5 years post-HSCT	Age at Transplant < 30 days (N = 10) n (%)	≥ 30 days (N = 6) n (%)	Total (N = 16) n (%)	p-value
Mobility				
Walks without assistance	5 (50)	1 (16.7)	6 (37.5)	0.02
Requires assistive device	4 (40)	0 (0)	4 (25)	
Wheelchair bound	1 (10)	5 (83.3)	6 (37.5)	
Communication				0.02
Verbal-normal	8 (80)	1 (16.7)	9 (56.3)	
Verbal-abnormal speech	2 (20)	2 (33.3)	4 (25)	
Requires assistive communicative device	0 (0)	2 (33.3)	2 (12.5)	
Noncommunicative	0 (0)	1 (16.7)	1 (6.3)	
Feeding				0.29
By mouth-independently	7 (70)	2 (33.3)	9 (56.3)	
By mouth-requires assistance	1 (10)	2 (33.3)	3 (18.8)	
Requires tube	2 (20)	1 (16.7)	3 (18.8)	
Solely via tube	0 (0)	1 (16.7)	1 (6.3)	
Outcomes at most recent follow-up	**Age at Transplant < 30 days (N = 10) n (%)**	**≥ 30 days (N = 6) n (%)**	**Total (N = 16) n (%)**	**p-value**
Mobility				0.01

Walks without assistance	4 (40)	1 (16.7)	5 (31.3)	
Requires assistive device	5 (50)	0 (0)	5 (31.3)	
Wheelchair bound	1 (10)	5 (83.3)	6 (37.5)	
Communication				0.02
Verbal-normal	8 (80)	1 (16.7)	9 (56.3)	
Verbal-abnormal speech	2 (20)	2 (33.3)	4 (25)	
Requires assistive communicative device	0 (0)	2 (33.3)	2 (12.5)	
Noncommunicative	0 (0)	1 (16.7)	1 (6.3)	
Feeding				< 0.01
By mouth, independently	9 (90)	1 (16.7)	10 (62.5)	
By mouth, requires assistance	0 (0)	1 (16.7)	1 (6.3)	
Requires tube	1 (10)	2 (33.3)	3 (18.8)	
Solely via tube	0 (0)	2 (33.3)	2 (12.5)	

Table 3. Secondary Functional Outcomes

Outcomes at 5 years post-HSCT	Age at Transplant		Total (N = 16)
	< 30 days (N = 10)	≥ 30 days (N = 6)	
	n (%)	n (%)	n (%)
Spasticity	8 (80)	6 (100)	14 (87.5)
Seizures	0 (0)	2 (33.3)	2 (12.5)
School Attendance			
Appropriate grade for age (or above)	8 (80)	3 (50)	11 (68.8)
Lower grade than expected for age	2 (20)	2 (33.3)	4 (25)
Does not attend	0 (0)	1 (16.7)	1 (6.3)
School Performance			
Regular, mainstream classes	4 (40)	2 (33.3)	6 (37.5)
Requires specialized resources	6 (60)	3 (50)	9 (56.3)
Does not attend	0 (0)	1 (16.7)	1 (6.3)
Hearing loss	0 (0)	0 (0)	0 (0)
Vision loss	0 (0)	0 (0)	0 (0)
Dental problems	10 (100)	6 (100)	16 (100)
Aspiration events	0 (0)	1 (16.7)	1 (6.3)
Bowel/Bladder incontinence	0 (0)	2 (33.3)	2 (12.5)
Outcomes at most recent follow-up	**Age at Transplant**		
	< 30 days (N = 10)	**≥ 30 days (N = 6)**	**Total (N = 16)**
	n (%)	**n (%)**	**n (%)**
Spasticity	8 (80)	6 (100)	14 (87.5)

Seizures	0 (0)	2 (33.3)	2 (12.5)
School Attendance			
Appropriate grade for age (or above)	8 (80)	3 (50)	11 (68.8)
Lower grade than expected for age	2 (20)	3 (50)	5 (31.3)
Does not attend	0 (0)	1 (16.7)	1 (6.3)
School Performance			
Regular, mainstream classes	3 (30)	2 (33.3)	5 (31.3)
Requiring specialized resources	7 (70)	3 (50)	10 (62.5)
Does not attend	0 (0)	1 (16.7)	1 (6.3)
Hearing loss	0 (0)	0 (0)	0 (0)
Vision loss	0 (0)	0 (0)	0 (0)
Dental problems	10 (100)	6 (100)	16 (0)
Aspiration events	0 (0)	2 (33.3)	2 (12.5)
Bowel/Bladder incontinence	0 (0)	2 (33.3)	2 (12.5)

FIGURE LEGENDS

Figure 1. Overall Survival for those who underwent transplantation at < 30 days and at ≥ 30 days of life, and for the entire cohort.

Figure 2. Primary outcomes by age at transplant: mobility status at 5 years post-transplant (a) and at most recent follow-up (b), communication abilities at 5 years post-transplant (c) and at most recent follow-up (d), and feeding abilities at 5 years post-transplant (e) and at most recent follow-up (f). Dotted lines mark 30 days of life, separating the 2 groups for comparison.

FIGURES

Figure 1. Overall Survival

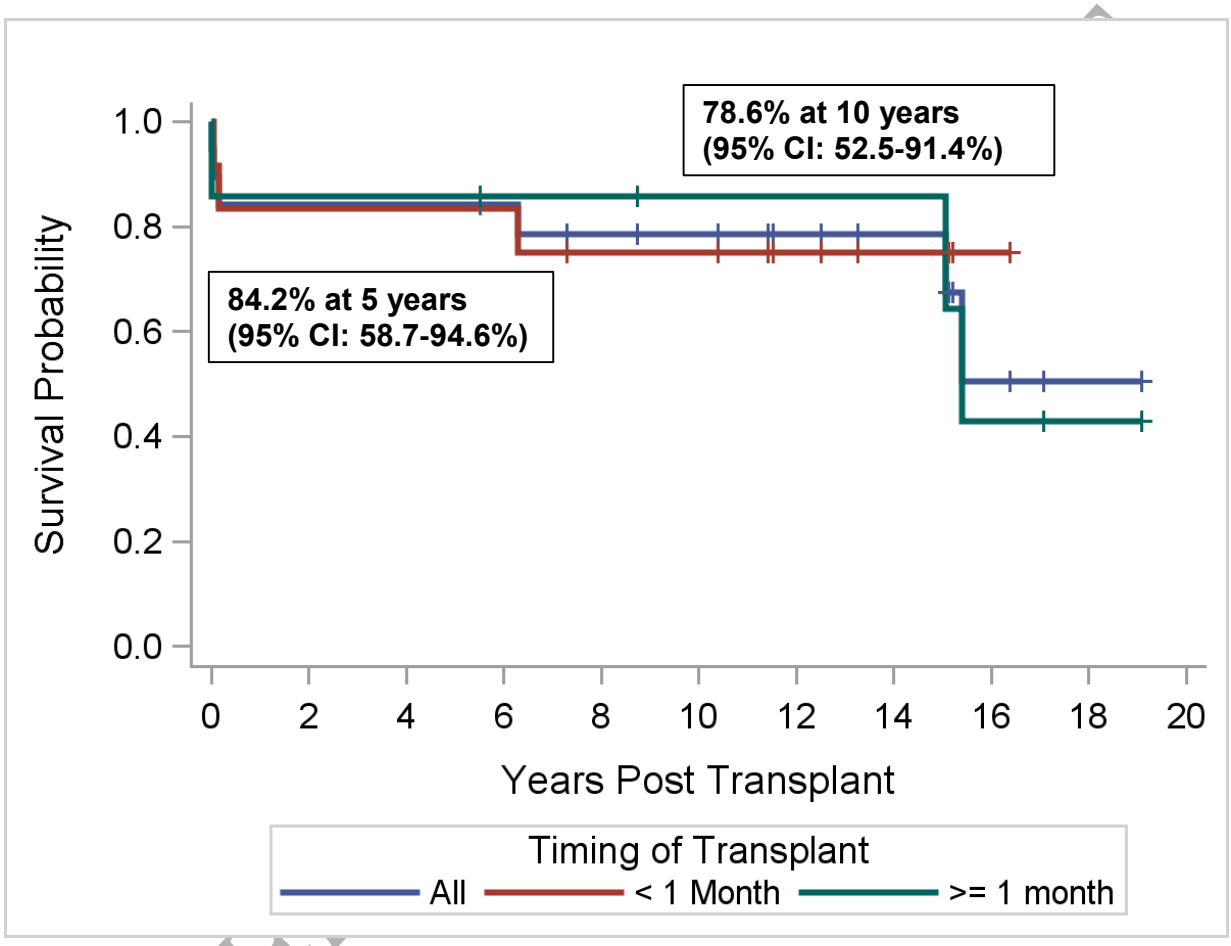
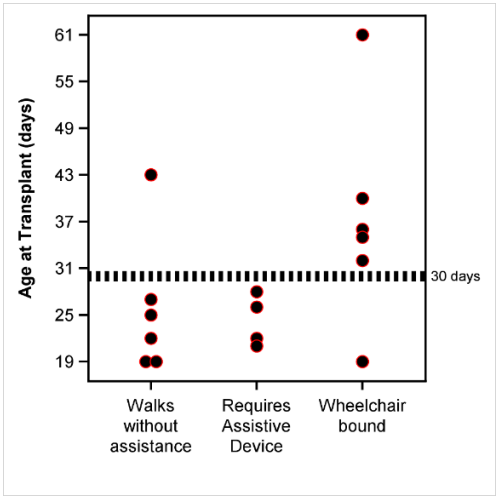
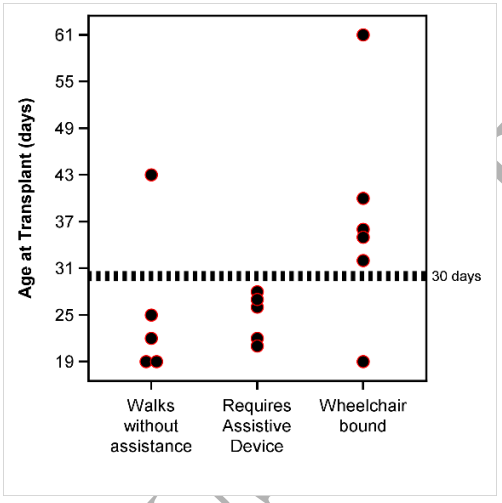


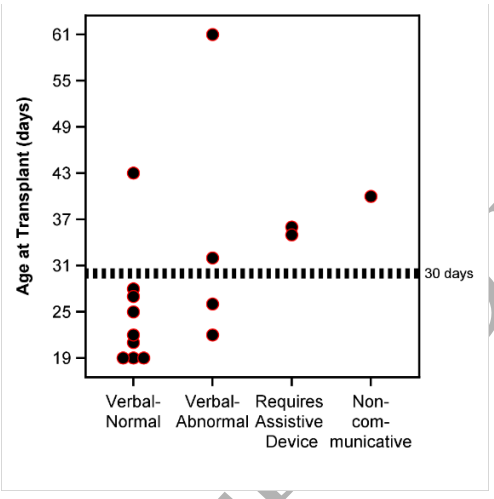
Figure 2. Primary Outcomes at 5 Years Post-Transplant and Most Recent Follow-up



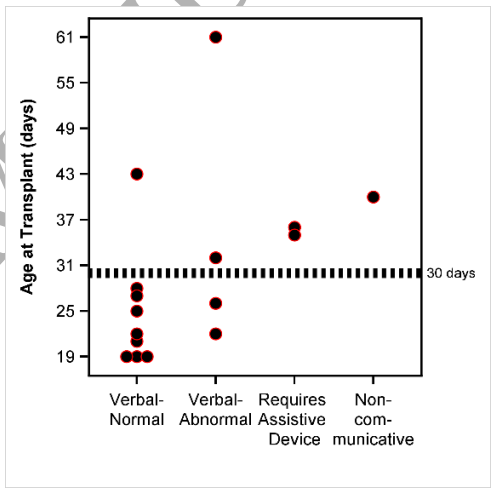
a.



b.

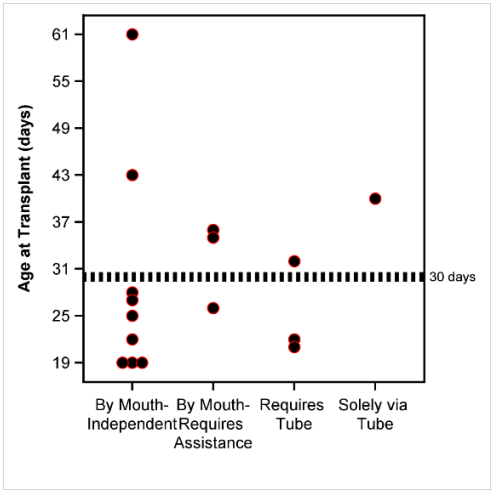


c.



d.

e.



f.