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Long-term Clinical Outcomes of Severe Combined Immunodeficiency Patients Given Nonablative Marrow Transplants

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Title: Long-term Clinical Outcomes of Severe Combined Immunodeficiency Patients
Given Nonablative Marrow Transplants

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Abstract**Background:**

Severe Combined Immunodeficiency (SCID) is a syndrome characterized by profound T cell deficiency that is universally fatal in infancy unless immune reconstitution is achieved by hematopoietic stem cell transplantation, gene therapy or enzyme replacement. Published long term clinical follow up is limited for transplanted SCID patients.

Objective:

To characterize the long-term outcomes of patients with SCID treated at a single center.

Methods:

We examined the clinical outcomes of 177 successive SCID infants given allogeneic bone marrow over 38 years without pre-transplant chemotherapy or post-transplant graft-versus-host disease (GVHD) prophylaxis. 90% received T cell-depleted haploidentical parental marrow. Clinical status was assessed by questionnaires delivered by mail or electronically. Molecular type of SCID, demographics, and type, date and age of transplant were obtained from a database.

Results:

Eighty-eight questionnaires were completed for survivors ranging in age from 2 to 38 years. Survival remained higher in those transplanted prior to 3.5 months of age. Half of the cohort remained on immunoglobulin replacement. Health conditions reported

included rashes, anxiety, depression, warts, and mouth ulcers. Most reported these were transient, self-resolving issues. Attention-deficit/hyperactivity disorder (ADHD), warts and learning disabilities were reportedly more prevalent than in the general population. Most reported having no active concerns about their health. We found substantial scholastic achievement, with half of adult patients reporting college attendance. Most patients had a healthy body mass index (BMI).

Conclusions:

Overall, our findings are consistent with those in the last update in 2009 in this population. Age at transplant remains a key variable in survival.

Highlights Box

1. What is already known about this topic?

Available long term outcome data about patients with Severe Combined Immunodeficiency are limited. Survival has previously been reported to be superior in infants transplanted early (< 3.5 mo).

2. What does this article add to our knowledge?

We continue to note better survival long term when transplanted early (< 3.5 mo). We found an overall higher prevalence of ADHD, warts and learning disabilities compared to the general population.

3. How does this study impact current management guidelines?

Early transplantation remains of key importance for survival. As the transplanted population ages, additional dermatologic and gynecologic monitoring may be warranted. Early assessment for learning disabilities and ADHD may be beneficial.

4. Key words:

Immunodeficiency, Hematopoietic stem cell transplantation, Severe Combined Immunodeficiency

Abbreviations

Severe Combined Immunodeficiency (SCID)

Interleukin 2 receptor gamma chain (IL2RG)

Graft-versus-host disease (GVHD)

Body-mass index (BMI)

Adenosine deaminase (ADA)

Attention-deficit/hyperactivity disorder (ADHD)

Hematopoietic stem cell transplantation (HSCT)

Matched unrelated donor (MUD)

Cartilage-Hair Hypoplasia (CHH)

Introduction

Severe Combined Immunodeficiency (SCID) is a genetic syndrome characterized by profound deficiency of T-cells (typically less than <300 cells/ μ l) and in some cases of B and/or NK cells.¹ Mutations in over 18 different genes have been identified as causative, and more will likely be described in the future.² The most common type of SCID is X-linked, which is due to interleukin 2 receptor gamma chain gene (*IL2RG*) mutations.

Patients with SCID are highly vulnerable to infections and this condition is universally fatal in the first or second year of life unless definitively treated. Hematopoietic stem cell transplantation has been the standard treatment for SCID,^{3,4,5} although there are now promising ongoing gene therapy trials for three molecular types of SCID⁶ and there is enzyme therapy available for ADA-deficiency.⁷ HLA-identical transplants are optimal, though not available in most cases. All transplants can be performed without pre-transplant chemotherapy because classical SCID patients lack T-cells and are not able to reject donor cells.⁸ Rigorous T-lymphocyte depletion of donor cells obviates the need for graft versus host disease (GVHD) prophylaxis.⁹ Circulating T-cells and T-cell function typically develop 90 to 120 days after transplantation.⁹ Survival rates are superior in infants who were transplanted prior to 3.5 months of age.¹⁰ Mazzolari et al reported that, although most patients attained normal T and B cell function after treatment, endocrine and severe neurologic abnormalities were observed in 17.5% and 10% of the patients, respectively.¹¹ Several studies reported neurologic complications in patients with adenosine deaminase (ADA) deficiency.^{12,13} However, long-term clinical outcome data are limited as this is the first generation of survivors with this previously fatal condition. An analysis of factors impacting survival of SCID infants after hematopoietic

cell transplantation over the last 4 decades in the US and Canada is ongoing by the Primary Immune Deficiency Treatment Consortium, sponsored by NIAID. This is a consortium of centers that do transplants in infants with SCID. In the first publication from this Consortium the most important factors influencing survival in transplants done from 2000 through 2009 were early diagnosis and freedom from infection.¹⁴ Since it has only been recently that newborn screening was approved in all states, it is likely too early to see the full impact of it. Two European studies, one by Antoine et al⁴ and another by Gennery et al¹⁵ reported that factors associated with improved overall survival were transplantation after the year 1995, genotypical or phenotypical donors, younger age at transplantation and absence of respiratory impairment or viral infection before transplantation.

The latest update on the Duke SCID cohort, the largest single center cohort worldwide, was last reviewed in 2009 by Railey et al.¹⁶ The overall survival rate was 77%. The survival rate at 8 years for the 48 infants transplanted in the first 3.5 months of life was 96%, compared with 70% for the 113 transplanted after 3.5 months ($p=0.002$). IVIG was being administered to 64 (58%) of the 111 patients, and about 1/3 of patients were on prophylactic antibiotics. Twenty-one percent of the patients had ADHD, with the highest proportion seen in ADA SCID. A majority of the surviving patients was considered by their family to be healthy. More than a decade since the last review, we report an update on the clinical status of the survivors ranging in age from toddler to 38 years old.

Methods

Prior to the study, we obtained approval by the Institutional Review Board (IRB) at Duke University Medical Center, and standards of medical ethics in research were followed as consistent with the Declaration of Helsinki.

We analyzed data on all successive patients with SCID who received bone marrow transplants at Duke University Medical Center from May 19, 1982 to August 1, 2019. Post-transplantation follow-up ranged from 8 days to 38 years. One hundred sixty of these patients received rigorously T-lymphocyte depleted haploidentical parental marrow, and 17 received HLA identical related bone marrow. No patient received pre-transplant chemotherapy or post-transplant GVHD prophylaxis. For transplantation of 159 of the haploidentical recipients, parental bone marrow was depleted of T cells by agglutination with soybean lectin and two cycles of rosetting with sheep erythrocytes treated with aminoethylisothiuronium bromide, as previously described.⁸ One haploidentical recipient received CD34 selected parental marrow cells.

Forty-eight patients were known to be deceased prior to the onset of the study. The remaining 129 patients or the caregivers of the pediatric patients were contacted by telephone to introduce them to the background of the study. Based on patient's preference, either an electronic or a paper questionnaire about their health was delivered to them between August 2019 and July 2020. Adult and pediatric questionnaires were distributed based on patients' age. Adults were at least 18 years old at the time of delivery of the questionnaire. A consent statement was included prior to the questionnaire, participation in the study was voluntary and consent was implied

by completion of the study. Molecular type of SCID, demographics, type of transplant and date and age at transplantation were obtained from a database. Upon receipt of the questionnaires, data were entered into a secure database. The patients we were unable to reach did not have up to date contact information available. An obituary search was also done.

Statistical analysis:

The data were summarized descriptively with mean, standard deviation, and range for continuous variables and with numbers and percentages for categorical variables. Patient survival was analyzed using Kaplan-Meier survival curves. Survival rates were compared between patients transplanted before 3.5 months of age and those transplanted after 3.5 months using log rank test. Relationship between survival and age of transplant as a continuous variable was analyzed using the Cox proportional hazards regression model. Comparisons between different genetic groups were done using chi-square test; if expected cell count was less than 5 then Fisher's exact test was used instead. All statistical tests were two-sided with alpha level of 0.05. No formal adjustment for multiplicity of analyses was performed. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Survival

The overall survival of the entire cohort of 177 patients is 73% (Figure 1). The survival rate for those who received haploidentical transplants is 70%, while 100% of the 18 who received HLA identical related transplants survive. Forty-nine or 27.7% percent of the entire cohort of 177 patients required one or more booster transplants and of those 27 survive. Booster transplants were given to those with inadequate immune reconstitution following the first transplant and these were primarily those with chronic viral infections and who were older at the time of the first transplant.¹⁷ Four of the patients underwent gene therapy elsewhere (two with ADA-deficiency in Italy¹⁸ and two with γ c-Def SCID at the NIH¹⁹). Gene therapy was successful in three of the four but unsuccessful in one γ c-Def patient who subsequently received a matched unrelated donor (MUD) transplant following reduced intensity conditioning. Three ADA-deficient patients are currently receiving polyethylene glycol modified bovine adenosine-deaminase (PEG-ADA), and one received a MUD bone marrow transplant elsewhere. Two Artemis-deficient patients subsequently required conditioned cord blood transplants. The length of follow up ranged from 8 days to 38 years post-transplantation (median follow up 13.9 years, 25th percentile 4.3 years, 75th percentile 21.2 years). For the patients who were transplanted in the first 3.5 months of life, the median follow-up time was 16.1 years (25th percentile 8.3 years, 75th percentile 22.4 years). In the group of patients who were transplanted after 3.5 months of age, median follow up was 12.8 years (25th percentile 3.1 years, 75th percentile 21.1 years). Survival was clearly superior (15-year Kaplan-Meier survival rate 94%, 95% CI: 82%-98%) in the 55 patients who received their transplants in the first 3.5

months of life, only 4 of whom failed to survive. By contrast, 15-year Kaplan-Meier survival rate was only 68% (95% CI: 59%-76%) in the 122 who were transplanted after 3.5 months of age. This difference in survival is statistically significant with a log rank p value of 0.0004. Overall, older age at transplant was associated with lower survival (p-value<0.0001), with a hazard ratio of 1.026 per 10-day increase in age at transplant (95% CI: 1.013-1.039).

Causes of Death

Forty-eight of the entire cohort of 177 patients have died, with 23 succumbing in the first year and 14 more between 1- and 5-years post-transplantation. A majority of the patients presented after 3.5 months of life with life-threatening opportunistic infections and many required ventilator support on arrival. There were seven late deaths (age 18 or above); one was an ADA-deficient SCID being treated with PEG-ADA who died at age 18 years with pulmonary hypertension. The second was an autosomal recessive SCID patient with unknown molecular cause who died at age 18 of autoimmune cytopenia. The third death was a patient with Artemis deficient SCID who died of staphylococcal septicemia at age 20. The fourth was an X-linked SCID who required IVIG, was non-adherent with the medication and died of lung disease at age 23. The fifth was an X-linked SCID who died of chronic pulmonary disease at age 24 years, the sixth was an X-linked SCID who died of a rectal carcinoma at age 32 and the seventh was an X-linked SCID who died of idiopathic liver disease at age 34. Thirty-two of the entire group of 48 deceased patients (67%) died from viral infections present at the time of diagnosis which continued chronically. Nine died of cytomegalovirus infection, nine

more with adenoviral infection, six with EBV lymphoproliferative disease, four with enteroviral infections, three with parainfluenza 3 infection, two with varicella, one with Herpes simplex infection and one with RSV infection. Some had more than one viral infection. Five died of pulmonary disease, two from candida sepsis, one from an unrelated mitochondrial defect, one with the nephrotic syndrome following chemotherapy given prior to referral, and one of veno-occlusive disease. No patient died of graft-versus-host disease.

Clinical Features

Ninety-two out of the presumed 129 survivors were located and eighty-eight questionnaires were completed. Respondents ranged in age from 2 to 38 years. Fifty-two were adults ≥ 18 years at the time of the questionnaire. Genetic defects were known for 87/88 patients. X-linked SCID was the cause in slightly over half (49/88) of the patients. Other genetic defects included deficiencies in IL-7R, ADA, JAK3, RAG-1, RAG-2, CD3 chains, Cartilage Hair Hypoplasia (CHH), Artemis, and CD45 (Figure 2).

Demographic information is shown in Table 1. Most patients were male (81%) and Caucasian (84%). Thirty-eight of the 88 patients were transplanted before 3.5 months of age and 50 were transplanted after. Seventy-seven received a haploidentical parental donor transplant while 11 received an HLA-identical related transplant. Sixty-nine underwent one transplant, while 19 received booster transplantations. All were transplanted without pre-transplant chemotherapy or post-transplant graft-versus-host disease (GVHD) prophylaxis.

Post-transplant, 44/88 patients reported continued treatment with immunoglobulin replacement. Eighteen used prophylactic antibiotics, 51 had received immunizations, and about 1/3 had received live vaccines. Sixty-three of 88 patients reported seeing an immunologist regularly. In the adult group, more than a third of the patients reported that they do not see an immunologist regularly. Twenty-five took no daily medications other than over-the-counter supplements or birth control. Forty-nine adult patients shared their height and weight and 31 (63%) had a healthy BMI (BMI 18.5-24.9). Thirteen (26.5%) were overweight (BMI > 24.9), 3 (6%) were obese (BMI > 30), and 2 (4%) were underweight (< 18.5). In pediatric patients, the mean age and sex-adjusted BMI was at the 51st percentile and only 4 had a BMI that was <5th percentile.

Common health conditions reported were similar to those in the general population and included rashes, depression, anxiety, warts and mouth ulcers (Figure 3). Most described these as transient, self-resolving issues. Thirty-six of 88 (41%) reported warts ranging in severity from a transient infection to a persistent medical problem affecting their quality of life. One patient reported a genital *Herpes simplex* infection requiring chronic Valacyclovir. Twenty-one (24%) reported a learning disability, 21 (24%) reported ADHD, and 19 (22%) reported anxiety. Fifty-four out of 86 (63%) reported having no active concerns about their health. Though immunoglobulin replacement, infections, hospitalizations, and comorbidities varied amongst various genetic subtypes of SCID, the number of patients with each subtype were small and differences were not statistically significant (Table 2).

Our cohort described significant scholastic achievement, with more than half of adult patients (28/50) reporting at least partial college attendance, 3 Masters/Doctorate degrees, 10 completed college, 15 are currently in college or had partial college attendance. Three had post-graduate education including doctorate level degrees. This can be compared to college enrollment as per the US Census Bureau's published data, which indicates 41% enrollment of adults age 18-24 years old.²⁰ Occupations in our cohort included physician, nurse, factory worker, musician, teacher, and engineer. Three patients reported having children.

Discussion

This study is a long-term clinical follow up of the largest single center cohort of SCID patients in the United States. All 177 SCID patients in this cohort were transplanted without pre-transplant chemotherapy or GVHD prophylactic immunosuppressive agents. This presents a unique opportunity to study long term outcomes without the confounding consequences of toxicities related to chemotherapy or immunosuppression. Overall, the current clinical update on the SCID patients in this cohort does not indicate that there have been many negative changes in the health of the survivors since the last update over a decade ago.¹⁶ We continue to see strong survival benefit in those that were transplanted before 3.5 months of age. Most patients or the families of the pediatric patients did not report active concerns about their health. SCID is not a homogeneous condition, thus there is phenotypic variation among health conditions within the cohort. Although our cohort is the largest population of SCID patients transplanted at a single medical center, we are limited in the small number of patients within the non-X-linked SCID genetic subgroups. The difference in the prevalence of the medical conditions reported among the various types of SCID was variable, but not statistically significant. We see a trend toward better overall clinical status in the IL-7R α -Deficient SCID patients (Table 2).

We note an increased prevalence of ADHD (24%) and learning disabilities (24%). Regarding ADHD, these data are higher than both the estimated national prevalence of ADHD in children (11%) and lifetime prevalence in adults aged 18 to 44 years (8.1%).^{21,22} Anxiety was also prevalent (22%), but similar to the NIH reported prevalence of 19.1% in the general population.²³ It is unclear why there is a higher

prevalence of ADHD and learning disabilities in this cohort. Titman et al²⁴ reported that the average IQ for patients with severe congenital immunodeficiency was lower than the population average and unaffected siblings. In that study, the underlying genetic defect, ADA deficiency and consanguinity were associated with worse prognosis but age at transplantation and conditioning treatments were not.²⁴ In our data, ADA patients did have a higher rate of learning disability than other groups, but other groups also had a higher rate than expected, including X-linked SCID patients, the most represented group in the cohort. However, since no one in this cohort had pre-transplant chemotherapy, we can ascertain that this is not related to myeloablative therapies. Despite the higher incidence of ADHD and learning disabilities, our patients continue to demonstrate high academic abilities in many cases. Due to the limitations of the nature of an individually reported questionnaire, severity of the ADHD was not assessed. We believe that the inclusion of the scholastic outcomes including education attained provides hope that there are many high achieving individuals in this cohort. However, scholastic achievement does not rule out adversity or additionally work that these individuals or may not have had to endure.

B-cell function remains a challenge post-transplantation as evidenced by about half of the cohort requiring immunoglobulin replacement therapy. Conditioning regimens have been proposed to improve these outcomes though even with conditioning regimens in place, B-cell recovery may not occur and there is concern for long term effects of conditioning regimens. Overall, the use of conditioning, in particular busulfan, is associated with a greater likelihood of B cell reconstitution.^{14,25}

In addition, use of busulfan has been implicated in a number of late adverse effects, including dental anomalies affecting secondary dentition²⁶, thyroid dysfunction²⁷, and growth failure in radiosensitive SCID²⁸.

The most important predictor of the likelihood of B-cell function recovery is the genetic phenotype of SCID. Patients with IL-7 receptor α , ADA, and CD3 chain gene mutations can have normal B-cell function after transplantation with only host B cells²⁹.

Gene therapy offers a new treatment option for certain types of SCID, but even though B-cell function recovery rates are superior compared to traditional SCT treatment, it is not universal.

Twenty-nine out of 36, or 81% of the patients who reported having problems with warts had the genetic defects associated with poor or reduced NK cell function. SCID genotypes with low NK cell, such as IL-2R γ - and JAK3-deficient SCID patients have been previously reported to be at higher risk of developing extensive cutaneous human papillomavirus-associated warts.^{30,31} This is a notable concern to monitor in the SCID population as the survivors age, routine dermatologic and gynecologic monitoring may be warranted. The effect of the introduction of HPV vaccinations needs to be investigated in the future.

Weaknesses of our study include single center analysis, questionnaire-based reporting and significant number lost to follow up. Questionnaires were designed to inquire regarding medical conditions prevalent in the general population as well as in immunodeficiency, but data are limited by the interpretations of the recipients and there are biases possible in a survey-type study. Lack of standardization for various

socioeconomic statuses and the potential developmental impact of isolation in an immunocompromised population or the effect of primary gene defects vs infections patients encountered cannot be discounted. We also had a significant number who were lost to follow-up given the long follow-up time frame. Despite these weaknesses our report is an important analysis of the largest and longest followed single center cohort of treated SCID patients to date.

With the emergence of gene therapy as a novel treatment for many genetic conditions including SCID, it is of utmost importance to understand the long-term outcomes and complications of SCID patient treated with hematopoietic stem cell transplant, the current mainstay treatment. The cohort of patients we report on has made remarkable progress surviving a previously invariably fatal condition. The aim of future efforts should be to continue to understand the changing needs of the aging SCID population and improve the available therapies for future generations.

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Figure captions

Figure 1. Kaplan Meier Survival Curves based on age at transplant with 95% confidence intervals. Patients transplanted at less than 3.5 months of age represented in blue.

Those transplanted at or greater than 3.5 months of age represented in red.

Figure 2. Genetic causes of SCID in the study population. X-linked SCID was the most common type in this study population.

Figure 3. Medical conditions reported by the 88 SCID patients who completed a questionnaire for this study, separated by age at transplanted. The only statistically significant difference ($p=0.006$) based on age at transplant was in the multiple transplants, 7.9% multiple transplants in those transplanted at < 3.5 months and 32% in those transplanted ≥ 3.5 months.

Table I. Demographic information of the 177 total patients with SCID analyzed in the cohort and the 88 of the 177 who completed a questionnaire.

Characteristic	Overall (n=177)	Questionnaire Participants (n=88)
Race, n/N(%)		
White	131/177 (74.0%)	74/88 (84.1%)
African American	27/177 (15.3%)	8/88 (9.1%)
Hispanic	16/177 (9.0%)	5/88 (5.7%)
Native American	3/177 (1.7%)	1/88 (1.1%)
Sex, n/N(%)		
F	36/177 (20.3%)	17/88 (19.3 %)
M	141/177 (79.7%)	71/88 (80.7%)
SCID type, n/N(%)		
X-Linked	82/177 (46.3%)	49/88 (55.7%)
ADA	26/177 (14.7%)	9/88 (10.2%)
IL-7R	25/177 (14.1%)	10/88 (11.4%)
JAK3	10/177 (5.6%)	7/88 (8.0%)
RAG1	3/177 (1.7%)	3/88 (3.4%)
RAG2	5/177 (2.8%)	3/88 (3.4%)
CD3	4/177 (2.3%)	3/88 (3.4%)
Artemis	7/177 (4.0%)	1/88 (1.1%)
ATM	1/177 (0.6%)	0/88 (0.0%)
Unknown Mutation	12/177 (6.8%)	1/88 (1.1%)
CD45	1/177 (0.6%)	1/88 (1.1%)
CHH	1/177 (0.6%)	1/88 (1.1%)
Transplant type, n/N(%)		
Haploidentical	160/177 (90.4%)	77/88 (87.5%)
Identical	17/177 (9.6%)	11/88 (12.5%)
Multiple transplants, n/N(%)		
One	128/177 (72.3%)	69/88 (78.4%)
Multiple	49/177 (27.7%)	19/88 (21.6%)
Age of questionnaire participants (years)		
N	177	88
Median (25th, 75th)	-	21.0 (14.0, 25.0)
Mean (SD)	-	20.3 (8.1)
Min, Max	-	2.0, 38.0
Age at transplant < 3.5 months, n/N(%)		
No	122/177 (68.9%)	50/88 (56.8%)
Yes	55/177 (31.1%)	38/88 (43.2%)

Abbreviations: F (female), M (male), Adenosine deaminase (ADA), Interleukin-7 receptor (IL-7R), JAK3 (Janus Kinase 3), RAG1 (Recombination Activating 1), RAG2 (Recombination Activating 2), ATM (ATM Serine/Threonine Kinase), CHH (cartilage-hair hypoplasia)

Table 2. Clinical characteristics of the surviving patients with SCID based on type of genetic defect.

Characteristic	Overall	X-Linked	ADA	IL-7R	JAK3	RAG-1	RAG-2	CD3	Artemis	CD45	CHH	Unknown	P-value	Test
Immunoglobulin replacement (current), n/N(%)	44/88 (50.0%)	31/49 (63.3%)	3/9 (33.3%)	0/10 (0.0%)	3/7 (42.9%)	1/3 (33.3%)	3/3 (100.0%)	0/3 (0.0%)	1/1 (100.0%)	1/1 (100.0%)	1/1 (100.0%)	0/1 (0.0%)	<.001	FISHER EXACT
On prophylactic antibiotics, n/N(%)	18/88 (20.5%)	10/49 (20.4%)	3/9 (33.3%)	0/10 (0.0%)	0/7 (0.0%)	1/3 (33.3%)	2/3 (66.7%)	1/3 (33.3%)	0/1 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)	0.091	FISHER EXACT
Warts, n/N(%)	36/88 (40.9%)	26/49 (53.1%)	1/9 (11.1%)	3/10 (30.0%)	2/7 (28.6%)	0/3 (0.0%)	0/3 (0.0%)	3/3 (100.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)	0/1 (0.0%)	0.017	FISHER EXACT
Sinus Infections in the last 2 years, n/N(%)	24/88 (27.3%)	17/49 (34.7%)	2/9 (22.2%)	1/10 (10.0%)	1/7 (14.3%)	1/3 (33.3%)	1/3 (33.3%)	1/3 (33.3%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0.909	FISHER EXACT
Pneumonia in the last 2 years, n/N(%)	8/88 (9.1%)	4/49 (8.2%)	1/9 (11.1%)	0/10 (0.0%)	1/7 (14.3%)	0/3 (0.0%)	1/3 (33.3%)	0/3 (0.0%)	0/1 (0.0%)	1/1 (100.0%)	0/1 (0.0%)	0/1 (0.0%)	0.256	FISHER EXACT
Hospitalization in the last 2 years, n/N(%)	14/88 (15.9%)	6/49 (12.2%)	3/9 (33.3%)	1/10 (10.0%)	1/7 (14.3%)	1/3 (33.3%)	2/3 (66.7%)	0/3 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0.326	FISHER EXACT
Learning Disability, n/N(%)	21/88 (23.9%)	12/49 (24.5%)	4/9 (44.4%)	1/10 (10.0%)	2/7 (28.6%)	0/3 (0.0%)	2/3 (66.7%)	0/3 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0.572	FISHER EXACT
Developmental Delay, n/N(%)	11/88 (12.5%)	5/49 (10.2%)	2/9 (22.2%)	1/10 (10.0%)	2/7 (28.6%)	1/3 (33.3%)	0/3 (0.0%)	0/3 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0.673	FISHER EXACT
ADHD, n/N(%)	21/88 (23.9%)	11/49 (22.4%)	4/9 (44.4%)	3/10 (30.0%)	2/7 (28.6%)	0/3 (0.0%)	1/3 (33.3%)	0/3 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0.892	FISHER EXACT
Anxiety, n/N(%)	19/88 (21.6%)	10/49 (20.4%)	3/9 (33.3%)	2/10 (20.0%)	1/7 (14.3%)	1/3 (33.3%)	1/3 (33.3%)	1/3 (33.3%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0.933	FISHER EXACT
Depression, n/N(%)	11/88 (12.5%)	7/49 (14.3%)	1/9 (11.1%)	0/10 (0.0%)	0/7 (0.0%)	1/3 (33.3%)	2/3 (66.7%)	0/3 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0.272	FISHER EXACT
Underweight, n/N(%)	6/82 (7.3%)	3/47 (6.4%)	0/8 (0.0%)	1/9 (11.1%)	0/7 (0.0%)	1/2 (50.0%)	1/3 (33.3%)	0/2 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0/1 (0.0%)	0.289	FISHER EXACT

Abbreviations: ADHD (Attention deficit hyperactivity disorder), Adenosine deaminase (ADA), Interleukin-7 receptor (IL-7R), JAK3 (Janus Kinase 3), RAG1 (Recombination Activating

1), RAG2 (Recombination Activating 2), ATM (ATM Serine/Threonine Kinase), CHH (cartilage-hair hypoplasia)

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Figure 1

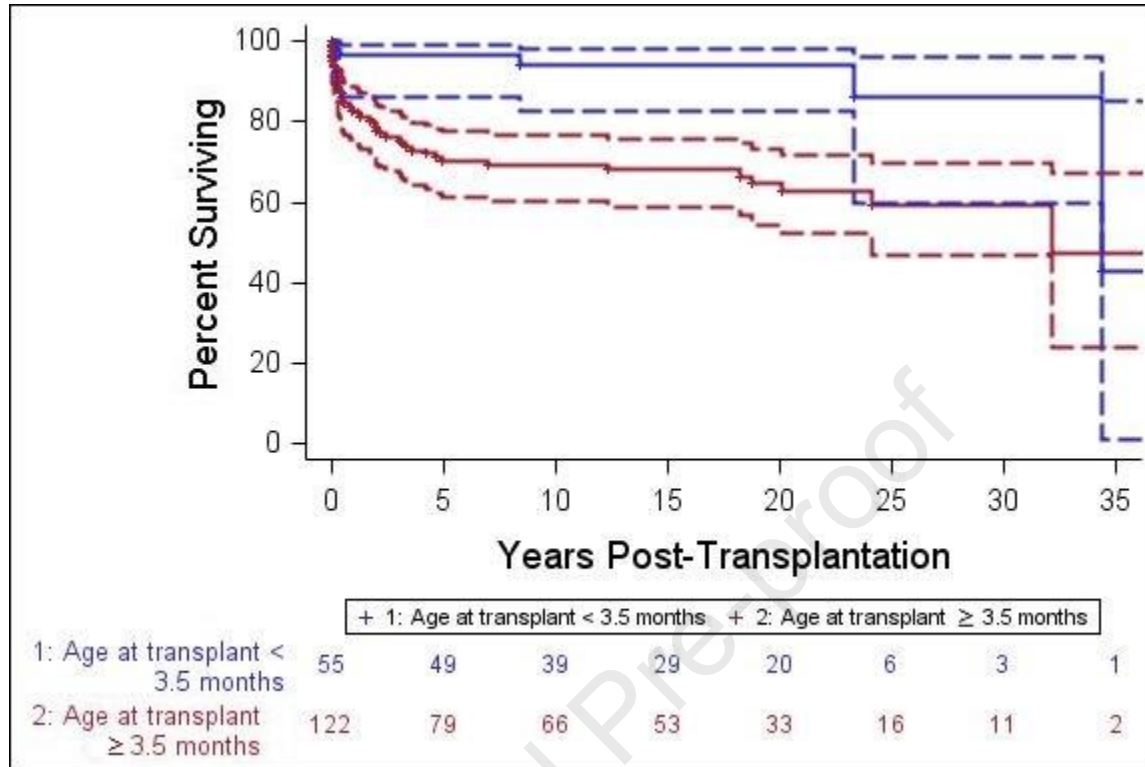
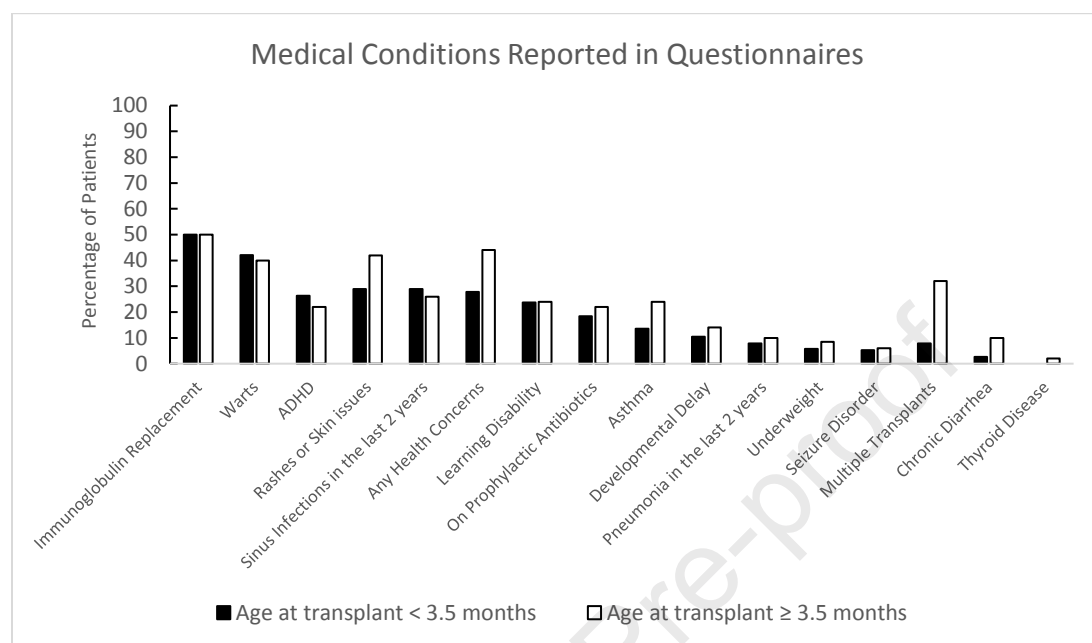


Figure 3.



Figures 2

