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ORIGINAL ARTICLE

Clinical and Laboratory Factors Affecting the Prognosis of Severe Combined Immunodeficiency

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Abstract

Purpose Severe combined immunodeficiency (SCID) is one of the most severe forms of inborn errors of immunity characterized by absence or loss of function in T cells. The long-term outcomes of all forms of SCID have been evaluated in a limited number of studies. We aimed to evaluate the pre- and post-transplant manifestations of SCID patients and determine the factors affecting the survival of patients.

Methods We included 54 SCID patients (classical SCID, Omenn syndrome, atypical SCID (AS)) in this study. We evaluated the clinical presentation, infections, and outcome of hematopoietic stem cell transplantation (HSCT). Lymphocyte subsets and T-cell receptor (TCR) repertoire were analyzed by flow cytometry.

Results The median age at diagnosis was 5 (range: 3–24) months and follow-up time was 25 (range: 5–61) months. Symptom onset and diagnostic ages were significantly higher in AS compared to others ($p = 0.001$; $p < 0.001$). The most common SCID phenotype was T-B-NK + , and mutations in recombination-activating genes (*RAG1/2*) were the prominent genetic defect among patients. The overall survival (OS) rate was 83.3% after HSCT, higher than in non-transplanted patients ($p = 0.001$). Peripheral blood stem cell sources and genotypes other than *RAG* had a significant favorable impact on CD4$^+$ T cells immune reconstitution after transplantation ($p = 0.044$, $p = 0.035$; respectively). Gender matching transplantations from human leukocyte antigen (HLA)–identical and non-identical donors and using peripheral blood stem cell source yielded higher B-cell reconstitution ($p = 0.002$, $p = 0.028$; respectively). Furthermore, receiving a conditioning regimen provided better B-cell reconstitution and chimerism ($p = 0.003$, $p = 0.001$). Post-transplant TCR diversity was sufficient in the patients and showed an equal distribution pattern as healthy controls. The OS rate was lower in patients who underwent transplant with active infection or received stem cells from mismatched donors ($p = 0.030$, $p = 0.015$; respectively).

Conclusion This study identifies diagnostic and therapeutic approaches predictive of favorable outcomes for patients with SCID.

Keywords Severe combined immunodeficiency · Bone marrow transplantation · Immune reconstitution · T-cell receptor repertoire · Prognosis

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Introduction

Inborn errors of immunity (IEI) are a group of diseases comprising over 450 different disorders, affecting the development and function of the immune system [1–3]. Severe combined immunodeficiency (SCID) is the most severe form of IEI, characterized by the absence or loss-of-function in T cells, accompanied by variable dysfunction of B and natural killer (NK) cells. SCID typically present early in life with severe infections and in the absence of corrective therapies, most notably hematopoietic stem cell transplantation (HSCT), they can be rapidly fatal. SCID has a diverse genetic etiology and to date, there are 18 known SCID-related genes [2, 3]. These gene defects can vary in their prevalence across different populations depending on genetic founder effects and the prevailing consanguinity rates, the latter factor being particularly relevant to the autosomal recessive forms of SCID, which are more prevalent than X-linked SCID [4, 5].

Typical SCID is defined as very low count of T lymphocytes ($CD3^+$ T < 300/mm^3), but in atypical SCID (AS), hypomorphic variants of the genes can allow a partial T-cell differentiation [6], and phenotypically those patients show more autoimmunities and granulomatous lesions [7]. The other rare form of the disease is Omenn syndrome, characterized by skin rash, caused by infiltration of activated oligoclonal autologous T lymphocytes, lymphoproliferation, eosinophilia, and high serum IgE levels. While the clinical spectrum of SCID forms is variable, the survival rates have been reported to be similar among patients [8, 9].

SCID is a pediatric emergency and the timing of HSCT or preexisting infections is strongly associated with the survival rate [10, 11]. Type of donor is also a significant predictor of outcome and survival rates are higher among recipients of grafts from matched sibling donors (MSDs) [8, 10]. Molecular defects also show a significant relationship with survival especially DNA cross-link repair 1C (*DCLRE1C*) and adenosine deaminase (*ADA*) mutations, which have poorer outcomes [8]. Different conditioning regimens, including myeloablative conditioning (MAC) and reduced intensity conditioning (RIC), can be associated with better T- and B-cell reconstitutions and outcomes for some SCID types [8, 12, 13]. Furthermore, conditioning is usually required for a normal B lymphocyte function after transplantation, especially in SCID with no B cells (recombination activating genes—*RAG1/2*, *DCLRE1C*) or non-functional B cells (Janus kinase 3—*JAK3*, interleukin-2 receptor gamma—*IL2RG*) [8, 10]. On the other hand, a bona fide factor associated with event-free survival is the development of a sufficiently diverse T-cell receptor (TCR) repertoire after HSCT. Thus, measuring TCR diversity can be helpful in determining the necessity of early intervention to stabilize the graft for successful immune reconstitution [14, 15]. Increasing awareness of SCID and knowing their natural history would be critical to achieve a timely diagnosis with desired outcomes. Therefore, well-defined, long-term studies are warranted to better characterize the diagnosis, treatment modalities, and factors influencing the prognosis of SCID, especially in regions with highly consanguineous marriages requiring early diagnosis.

Herein, we surveyed the clinical and laboratory features of a cohort of Turkish SCID patients and provided detailed analyses of their immune reconstitution, chimerism, and TCR repertoire following HSCT, aiming to determine the factors affecting prognosis. In this context, by focusing on our geographic region, the present study is one of the largest and detailed cohorts evaluating SCID forms altogether.

Materials and Methods

This cohort comprises 54 SCID patients who were followed up at Marmara University Hospital, Division of Pediatric Allergy and Immunology between 2008 and 2021. We performed pre- and post-transplant evaluations for salient clinical phenotypes and immune reconstitution of patients. Detailed lymphocyte subsets were performed at admission; 3rd, 6th, and 12th months of transplantation; and at the final evaluation visit during the study. The TCR repertoire was analyzed in cases who completed the first year of HSCT and compared with healthy age-matched donors. The study protocol was approved by the local ethics committee of Marmara University Faculty of Medicine Ethics Committee (09.2019.511) and written informed consent was obtained from all parents.

Clinical Evaluation and Transplantation Features

Clinical characteristics, including age at presentation, age at symptom onset, infections, involved systems, and treatment regimens, were identified for every patient. Clinical and molecular diagnoses of SCID were established based on the International Union of Immunological Societies (IUIS) and the Primary Immune Deficiency Treatment Consortium (PIDTC) criteria [2, 6]. We evaluated HSCT features in terms of donor type, degree of HLA match, stem cell source, infection status, conditioning regimens, immune reconstitution, chimerism rates, and complications. T-cell compartment recovery was defined as $CD3^+$ T-cell counts > 1000/mm^3 and $CD4^+$ T-cell counts > 500/mm^3. B cell compartment recovery was defined as $CD19^+$ B-cell counts > 400/mm^3 with the added stipulation of detectible serum IgA level and independence from immunoglobulin replacement therapy (IgRT).

Immunological Assessments

Peripheral lymphocyte subset and TCR Vβ repertoire analyses were performed by flow cytometry. Whole blood was incubated with monoclonal antibodies against surface markers in the dark at room temperature for 20 min. After lysis of erythrocytes, cells were washed and proceeded with flow acquisition [16–18]. Beta Mark TCRVβ repertoire kit staining was performed according to the manufacturer's instructions (Beckman Coulter, FR). Stained cells were acquired with FACSCalibur (Becton Dickinson) and Navios EX cytometer (Beckman Coulter). Cytobank software (Beckman Coulter) was used to analyze the available pre- and post-transplantation samples with Navios Ex cytometer.

Statistical Analysis

We used descriptive statistical parameters such as percentage, median with interquartile range (IQR), and mean with standard deviation during the study. Kolmogorov–Smirnov distribution test was conducted to determine the normal distribution of the analyzed data. Fisher's exact test was used for the comparison of categorical values. Mann–Whitney *U* test and 1-way ANOVA with Tukey's post hoc test analysis were performed to compare continuous values between groups and the Wilcoxon sign test was used for intragroup comparisons. Survival analysis was performed by Kaplan–Meier analysis. Cox regression analysis was used to evaluate the factors affecting survival. A statistical significance was considered at a $p\text{-value} < 0.05$. Statistical analysis was done using GraphPad Prism 9 (GraphPad Software Inc., San Diego, CA) and SPSS 20 (IBM, Chicago, IL, USA).

Results

Demographic Characteristics of the Patients

A total of 54 patients, including 19 (35.2%) females and 35 (64.8%) males, were entered into this study, with a median current age of 33 months (IQR 8–86). According to the classification of PIDTC, 28 (51.8%) of 54 patients were

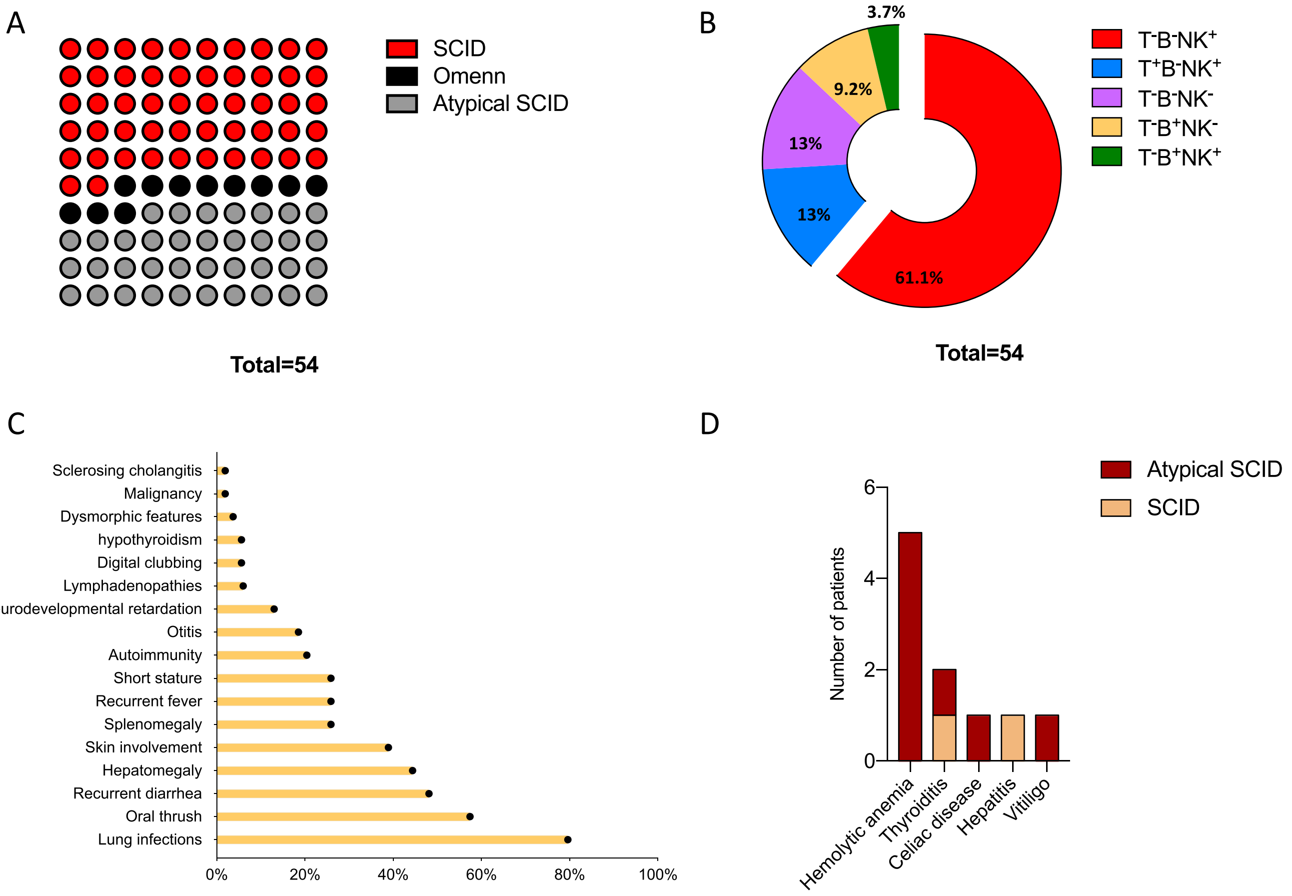

Fig. 1 The distribution of patients and prominent clinical features. **A** Dot plot graph showing the patients' number of three groups of disease. **B** The frequency of immune phenotype observed in the cohort. **C** The percentages of disease symptom clusters. **D** The frequency of autoimmune manifestations detected in the patients with SCID and AS

Table 1 Demographic, clinical presentations, and outcomes of the patients

Patient	Subgroup	Genetic defect	Gender	Diagnostic age (month)	Age at onset (month)	Consanguinity	Pneumonia	Moniliasis	Diarrhea	Skin involvement	Other clinical findings	Isolated agents	Last follow-up
P1	SCID	Undetermined	Male	4	3	+	+	+	-	-	HSM, hemophagocytic syndrome	CMV	Deceased/4.5 months
P2	SCID	Undetermined	Female	2	0	+	+	+	+	+	LAP, hepatomegaly	*Klebsiella pneumonia*	Deceased/7 months
P3	SCID	Undetermined	Male	5	4	+	+	+	+	-	Autoimmune thyroiditis	*Enterococcus faecium*, *Aspergillus fumigatus*	Deceased/60 months
P4	SCID	Undetermined	Female	7	6	+	+	+	-	-	-	*Mycobacterium tuberculosis*, CMV	Deceased/10 months
P5	SCID	*FOXN1*	Male	3	1	-	+	+	+	-	Otitis media	*Staphylococcus Hominis*	Deceased/3 months
P6	SCID	Undetermined	Male	7	3.5	+	+	+	-	-	HSM	-	Deceased/8 months
P7	SCID	*IL2RG*	Male	3	1.5	-	+	+	+	-	-	-	Deceased/4 months
P8	SCID	*PNP*	Male	24	6	+	-	-	+	-	Orbital fungal infection, diffuse large B-cell lymphoma, sepsis	*Escherichia coli*, *Aspergillus spp.*, EBV	Deceased/31 months
P9	SCID	*DCLRE1C*	Female	3	3	+	+	+	-	-	-	-	Deceased/28 months
P10	SCID	Undetermined	Male	7	0	+	+	+	-	+	Septic arthritis	*Acinetobacter*, Varicella zoster virus, CMV	Deceased/15 months
P11	SCID	Undetermined	Male	4	3	+	-	+	-	-	LAP, hepatomegaly	*Enterococcus faecium*, *Aspergillus fumigatus*	HSCT/alive
P12	SCID	*ADA*	Male	6	1	+	+	+	-	-	Otitis media	*Acinetobacter baumannii*	HSCT/alive
P13	SCID	Undetermined	Male	4	1	+	+	+	+	-	Myocarditis	CMV	HSCT/deceased/6 months
P14	SCID	Undetermined	Male	1	1	+	-	-	+	-	Thyroiditis	CMV	HSCT/deceased/7 months
P15	SCID	Undetermined	Male	0	0	+	+	-	-	-	HSM	*Acinetobacter baumannii*, *Staphylococcus Hominis*	HSCT/alive
P16	SCID	*ADA*	Male	2	1.5	+	+	+	-	+	-	*Staphylococcus Hominis*, CMV	HSCT/alive
P17	SCID	*ADA*	Male	0	0	+	+	+	-	-	Herpetic keratitis	CMV, *Klebsiella Pneumonia*	HSCT/deceased/9 months
P18	SCID	*IL2RG*	Male	3.5	3	-	+	-	+	+	Hemophagocytic syndrome, herpetic keratitis	CMV	Deceased/8 months
P19	SCID	*DCLRE1C*	Male	4	1	+	+	+	-	+	-	CMV	HSCT/deceased/11 months
P20	SCID	Undetermined	Female	0	0	+	-	-	-	-	-	-	HSCT/alive
P21	SCID	*RAG1*	Female	2	1	-	-	+	+	-	Sepsis	CMV	Deceased/3 months
P22	SCID	Undetermined	Female	4	2	+	+	+	+	-	Hemophagocytic syndrome	*Staphylococcus haemolyticus*, CMV	HSCT/alive
P23	SCID	Undetermined	Female	3	2	+	+	+	+	-	Anal abscess	-	HSCT/alive
P24	SCID	*IL7Ra*	Female	3	1	+	+	+	+	-	-	-	HSCT/alive
P25	SCID	*PNP*	Male	15	6	+	+	+	+	-	-	CMV	HSCT/alive
P26	SCID	*DCLRE1C*	Male	3.5	1.5	+	+	+	+	+	-	*Staphylococcus Aureus*, CMV	HSCT/alive
P27	SCID	Undetermined	Male	4	2	+	-	-	-	-	Autoimmune hemolytic anemia, thrombocytopenia	-	HSCT/alive
P28	SCID	Undetermined	Female	3	2.5	+	-	+	+	-	-	CMV	HSCT/alive
P29	Omenn	*RAG1*	Female	2	0	+	+	-	+	+	Hepatomegaly	*Staphylococcus haemolyticus*	Deceased/3 months
P30	Omenn	*RAG1*	Female	1	0	+	+	+	-	+	CMV pneumonia, hemophagocytosis	CMV	Deceased/3 months
P31	Omenn	*RAG2*	Male	3	1	+	+	+	-	+	LAP, hepatomegaly	*Pseudomonas aeruginosa*	HSCT/alive

Table 1 (continued)

Patient	Subgroup	Genetic defect	Gender	Diagnostic age (month)	Age at onset (month)	Consanguinity	Pneumonia	Moniliasis	Diarrhea	Skin involvement	Other clinical findings	Isolated agents	Last follow-up
P32	Omenn	Undetermined	Male	2	0	+	-	-	-	+	Congenital nephrotic syndrome	*Staphylococcus Aureus*	HSCT/deceased/3 months
P33	Omenn	*RAG2*	Female	4	2	+	+	-	-	+	LAP, hepatomegaly	CMV	HSCT/alive
P34	Omenn	*RAG1*	Female	1	0.5	-	+	-	-	+	Hepatomegaly Splenomegaly	-	HSCT/alive
P35	AS	*RAG2*	Male	5	0	-	+	+	+	+	CMV pneumonia and colitis, skin abscess, myelodysplasia, sepsis	*Pseudomonas aeruginosa*, CMV	Deceased/40 months
P36	AS	Undetermined	Male	96	84	+	+	-	-	-	Osteomyelitis, sepsis	CMV	No HSCT/alive
P37	AS	Undetermined	Male	40	2	+	+	-	-	-	Autoimmune hemolytic anemia, invasive pulmonary aspergillosis	CMV, *Aspergillus spp.*	Deceased/44 months
P38	AS	*RAG1*	Male	132	30	-	+	-	-	-	Herpes infection, autoimmune hemolytic anemia	*Pseudomonas aeruginosa*, CMV	No HSCT/alive
P39	AS	*RAG1*	Female	108	60	+	+	-	+	+	Nephrotic syndrome, amyloidosis, autoimmune hemolytic anemia, sepsis	CMV	Deceased/138 months
P40	AS	*DCLRE1C*	Male	56	24	+	+	-	+	-	Myocarditis, autoimmune hemolytic anemia	CMV	No HSCT/alive
P41	AS	Undetermined	Female	84	80	+	+	-	-	-	-	CMV	No HSCT/alive
P42	AS	*ATM*	Male	7	2	+	+	+	+	+	BCGitis	*Staphylococcus aureus*, *Klebsiella pneumonia*, CMV	No HSCT/alive
P43	AS	*ADA*	Male	10	0.5	-	+	+	+	+	-	*Klebsiella pneumonia*, CMV	HSCT/alive
P44	AS	*DCLRE1C*	Male	63	36	-	+	-	-	-	-	CMV	HSCT/alive
P45	AS	*RAG1*	Female	42	0.5	+	+	+	-	+	BCG lymphadenitis, hypothyroidism, vitiligo HSM	*Moraxella Catarrhalis*, CMV	HSCT/alive
P46	AS	*RAG2*	Male	46	12	+	+	-	+	-	Autoimmune enteropathy, skin abscess	*Aspergillus spp.*	HSCT/alive
P47	AS	*ADA*	Female	15	12	+	+	+	+	+	-	CMV	HSCT/alive
P48	AS	*RAG1*	Female	44	12	+	+	-	+	-	Autoimmune hemolytic anemia	*Haemophilus influenzae*, CMV	HSCT/alive
P49	AS	*RAG2*	Male	70	60	+	+	-	-	+	-	-	HSCT/alive
P50	AS	Undetermined	Male	4	3	+	+	-	-	+	-	CMV	HSCT/alive
P51	AS	Undetermined	Male	11	3	+	+	+	-	+	-	*Staphylococcus hominis*, *Staphylococcus Haemolyticus*, CMV	HSCT/alive
P52	AS	*IL2RG*	Male	342	24	-	+	-	-	-	Recurrent otitis media	*Aspergillus spp.*	No HSCT/alive
P53	AS	*NHEJ1*	Male	7	1.5	+	+	+	+	-	-	-	Deceased/100 months
P54	AS	*NHEJ1*	Female	24	4	+	-	-	+	-	Recurrent otitis media	-	HSCT/alive

ADA, adenosine deaminase; *ATM*, ataxia telangiectasia mutated; *BCG*, bacillus Calmette–Guerin; *CMV*, cytomegalovirus; *DCLRE1C*, DNA cross-link repair 1C; *FOXN1*, forkhead Box N1; *HSM*, hepatosplenomegaly; *IL2RG*, interleukin 2 receptor subunit gamma; *IL7R*, interleukin 7 receptor; *LAP*, lymphadenopathy; *NHEJ1*, non-homologous end-joining factor 1; *PNP*, purine nucleoside phosphorylase; *RAG*, recombination activating gene classified as classical SCID, six as Omenn (11.1%), and 20 (37%) as atypical SCID (AS) (Fig. 1A, Table 1). The distribution of the immune subtypes is presented in Fig. 1B. Overall, 44 (81.5%) of the patients were a product of consanguineous marriages. The median age at symptom onset was 1.5 months in patients with classical SCID and 0.25 months in Omenn, both significantly were lower than in AS patients (12 months, $p = 0.001$ and $p = 0.003$; respectively, Table S1). The median duration for the delay in diagnosis in all groups was 3 months (IQR 1–10), and it was longer in AS patients (23.5 months) than in Omenn (2 months) and SCID (2 months) patients ($p = 0.001$, $p = 0.001$; respectively). The overall survival rate was 57.4% (31/54) and the non-transplant survival rate was higher in AS (60% (6/10)) than SCID patients ($p = 0.040$), while there were no surviving patients with SCID and Omenn without HSCT. The genetic diagnosis of the patients is presented in Table S2. The most common identified genetic defect was *RAG*1/2, while novel mutations in already established SCID genes were detected in 13 patients.

Clinical Findings of SCID Patients

Respiratory infections were the most common presenting complaint and observed in 43 (79.6%) of patients, followed by oral thrush ($n = 31$, 57.4%), diarrhea ($n = 26$ 48.1%), and skin involvement ($n = 21$, 38.9%). The clinical findings of the patients are presented in Fig. 1C. While oral thrush was observed more frequently in SCID compared to AS ($n = 22$, 78.6% vs $n = 7$, 35%, $p = 0.020$), short stature was higher in AS ($n = 10$, 50%) than in classical SCID patients ($n = 4$, 14.3%) due to older age presentation ($p = 0.001$, Table S1). Dysmorphic features were found in two patients (3.7%) (NHEJ1 deficiency). The incidence of autoimmunity was significantly higher in AS ($n = 8$, 36.8%) compared to classical SCID patients ($n = 2$, 7.1%) ($p = 0.016$, Fig. 1D). Blood CMV PCR positivity was detected in 30 patients (55.6%) at the time of diagnosis, higher in AS ($n = 15$, 75%) compared to SCID patients ($n = 12$, 43%) ($p = 0.024$). In total, 16 (29.6%) patients received BCG vaccination before diagnosis at 2 months of age according to the National Immunization Schedule, five of them developed BCGitis (9.3%, P4, P11, P42, P45, P50). The spectrum of infections and complications is presented in Table 1.

Immunological Assessments of the Patients

Detailed comparisons of lymphocyte subtypes of all patients are provided in Table S3. Paired comparisons of lymphocyte subsets in successfully transplanted patients ($n = 25$) are presented in Fig. 2. The lymphocyte counts in SCID patients were generally below 1500/mm^3 (93%), significantly lower than in Omenn and AS ($p = 0.01$, $p = 0.005$; respectively), and increased after HSCT (Fig. 2A). Increases in the absolute number of CD3$^+$, CD4$^+$, and CD8$^+$ T cells with restoration of the naïve T-cell pool and improvement of B-cell counts were observed in SCID and AS patients following transplantation; however, several patients remained with low B cell count after HSCT (Fig. 2B–F). The phenotypic composition of cells was further evaluated by visualization tools developed to manage high-dimensional data (t-distributed stochastic neighbor embedding (t-SNE) and self-organizing map (SOM)), allowing a 2-dimensional visualization whereby phenotypically similar cells form a cluster. The t-SNE analysis demonstrated normal development of T, B, and NK cells after transplantation when compared to the cell clusters before transplantation, which were scarcely detected, and healthy controls (Fig. 3A). The detailed T-cell subsets analysis clearly showed a corrected cellular phenotype after transplantation when compared to the healthy controls (Fig. 3B–C).

Hematopoietic Stem Cell Transplantation

HSCT was performed on 30 patients (55.6%, Table 2). All of the patients except one were transplanted after 3 months of age. AS (72.3 ± 77.7 months) patients were transplanted later than in classical SCID (7.1 ± 5.7 months) and Omenn (4.2 ± 2.0 months) ($p < 0.001$, $p = 0.007$; respectively). The median of post-transplant follow-up was 25 months (IQR 6–58) with an overall survival (OS) after transplantation as 83.3% (25/30). In total, five patients died after HSCT (P13, P14, P17, P19, P32), three of them due to pneumonia and respiratory failure (P13, P14, P17). P13 and P14 also developed graft rejections at 2.5 and 4 months, respectively. P17 had an uncontrolled systemic CMV infection. P19 experienced a severe gastrointestinal bleeding, leading to hemorrhagic shock and death. P32 showed a graft rejection and died after transplant-related acute lung injury (TRALI). In our cohort, there were 24 patients without transplantation and 19 (79.1%) of them deceased before transplantation with a median of 9 months (IQR 3–138). More specifically, eight died due to severe pneumonia (P2, P6, P7, P9, P29, P30, P37, P53), two with hemophagocytic lymphohistiocytosis (P1, P18), and five because of sepsis (P8, P21, P35, P36, P39). P3, P4, P5, and P10 died without known causes since the families refused treatment and transplantation. P38, P40, and P52 were not transplanted due to severe lung disease and failure to thrive. P41 was an AS with controlled disease manifestations under antimicrobial prophylaxis and IgRT. P42 was diagnosed with ataxia telangiectasia with no indication of HSCT.

Donors, Stem Cell Source, Conditioning, and Complications

Donors were predominantly HLA-matched ($n = 24$, 80%), distributed as matched related donor (MRD, $n = 7$), MSD

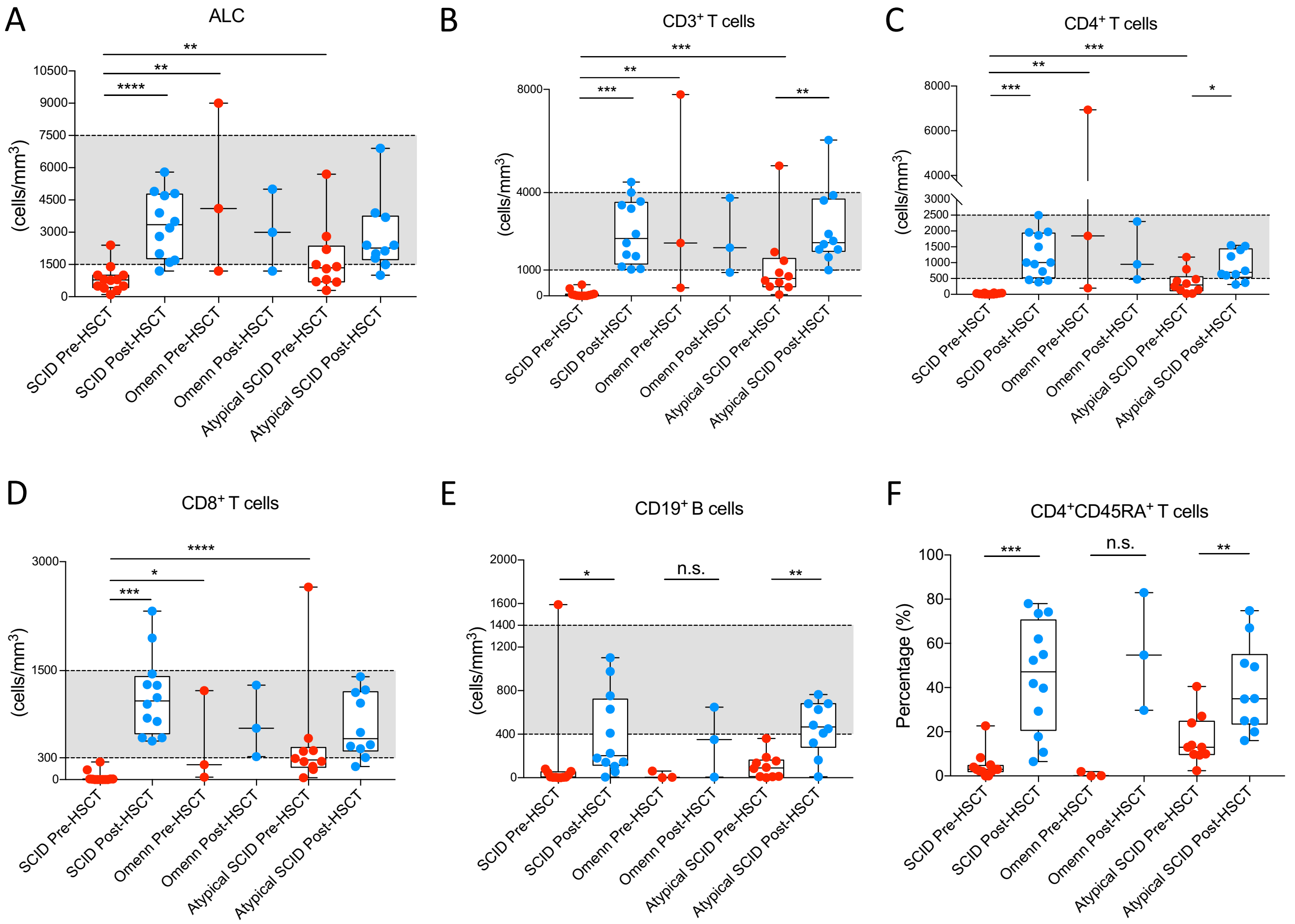

Fig. 2 SCID patients demonstrate a more severe immune phenotype compared to Omenn and AS, corrected successfully after HSCT. Box plot graphs of alive patients after transplantation (n:25) exhibiting the absolute numbers of lymphocyte (**A**), CD3$^+$ T cells (**B**), CD4$^+$ T cells (**C**), CD8$^+$ T cells (**D**), CD19$^+$ B cells (**E**), and the percentage of CD4$^+$CD45RA$^+$ cells (**F**). Mann–Whitney *U* test and Wilcoxon sign test were used. Asterisks indicate significance levels (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$). ALC, absolute lymphocyte number

($n = 9$), and matched unrelated donor (MUD, $n = 8$). Mismatched related donors (MMRD, $n = 6$; 20%) were used infrequently among patients (Table S4). There were 15 gender-matched donors, which were more common in AS compared to SCID patients ($n = 8$, 72.7% vs $n = 6$, 22.2%; $p = 0.008$). Bone marrow (66.7%) was frequently used as stem cell source, while peripheral blood stem cells were used in 23.3% of the patients. The MAC regimen, comprising busulfan and fludarabine, was applied in 11 (36.7%). Five (16.7%) patients received a reduced toxicity conditioning regimen as treosulfan and fludarabine combination, whereas two (6.7%) patients received a RIC (Table 2). The rest of the patients ($n = 12$, 40%) were transplanted without conditioning, an approach that was prominent in the classical SCID group (Table S4). Graft versus host disease (GvHD) was observed in 11 (36.6%) patients, including nine with acute and four with chronic GvHD. Two patients experienced acute and chronic GvHD. The rate of GvHD was not associated with stem cell sources ($p > 0.05$).

Twenty-two (73.3%) patients developed infections after transplantation despite antimicrobial prophylaxis. These infections included CMV reactivation in 12 (40%), sepsis in six (20%), and pneumonia in five (17%) patients. *Klebsiella pneumonia*, *Acinetobacter baumannii*, *Candida albicans*, and *Pseudomonas aeruginosa* were isolated from patients during sepsis, and there were no differences between groups regarding infections rate ($p > 0.05$).

Eight patients (26.6%) experienced post-transplantation complications including deep vein thrombosis (P14, P23), acute renal failure (P14), venoocclusive disease (P23), nephrotic syndrome (P16), pericardial effusion (P23), graft rejection and TRALI after a second transplantation (P32), and osteomyelitis (P48).

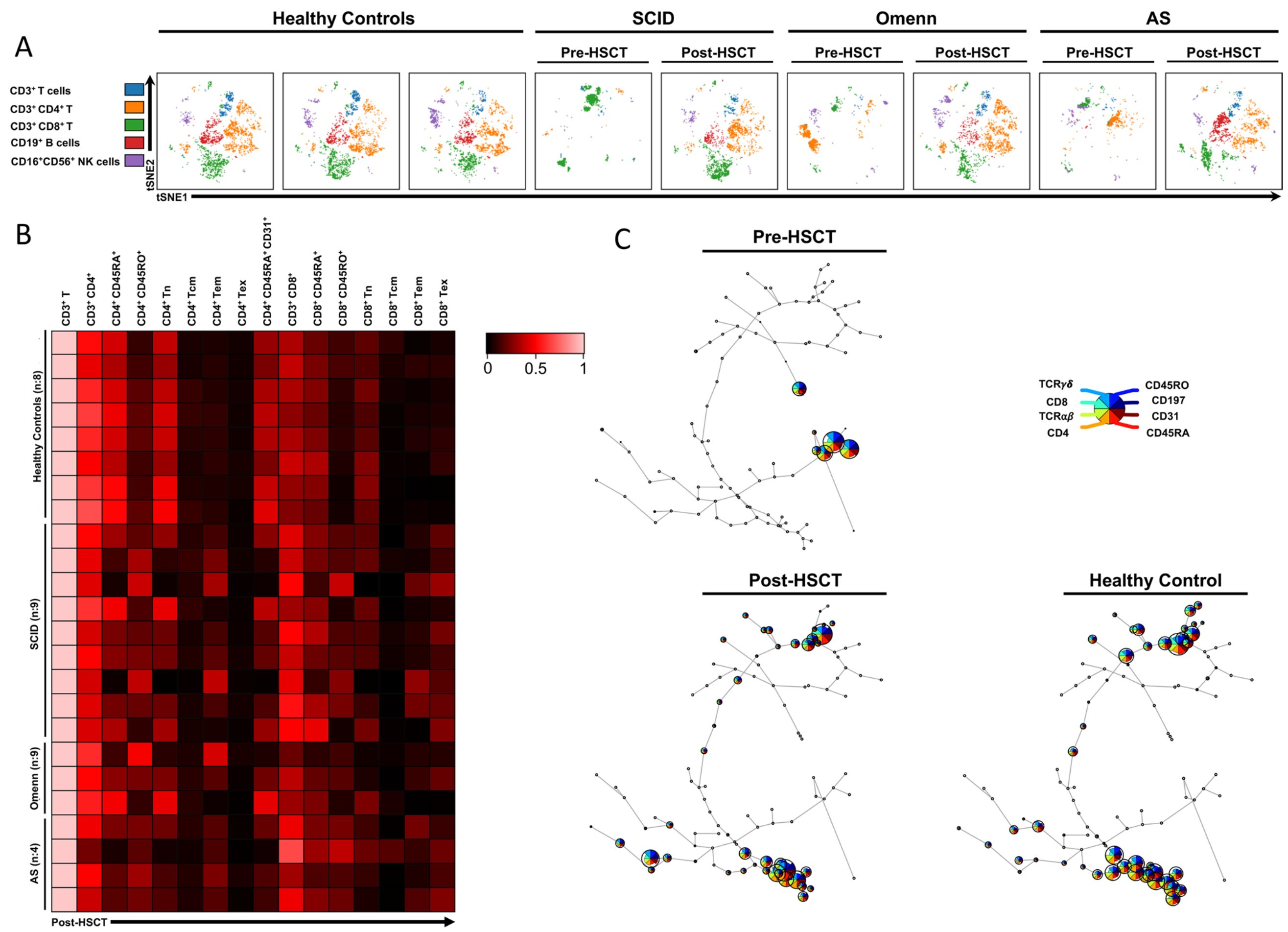

Fig. 3 Rescued immune profiles of the patients after transplantation. **A** A dimensional reduction analysis showing the comparison of T, B, and NK cells before and after transplantation. Representative analyses of SCID (P27), Omenn (P34), and AS (P47) are shown, **B** Normalized T-cell profile after transplantation evaluated by t-SNE analysis. Heatmap of the population abundance of individual clusters is presented for SCID subgroups and healthy controls. The equal selected event count of CD3$^+$ T-cell population was accepted as control and displayed with 1 point. The event counts of the other populations were quantified in folding ratio as divided to CD3$^+$ T-cell population. The results demonstrate similar distribution in patients after transplantation and healthy controls, **C** FlowSOM star plots analysis showing normalized T-cell clusters after transplantation compared to healthy controls. Colors in the individual clusters (P27) indicate the intensity of CD4$^+$, CD8$^+$, TCR$^{\alpha\beta/\gamma\delta}$, CD45RA$^+$, CD45RO$^+$, CD31$^+$, and CD197$^+$ in T cells. The star plots indicate the mean intensities of all clustering markers for all cells in CD3$^+$ T-cell cluster. The height of each segment indicates the intensity and if the segment reaches the border of the circle, the cells have high expression for that marker

Immune Reconstitution

During the evaluation, there were nine patients within the first year of transplantation, while 21 patients were beyond 1 year. The T- and B-cell reconstitution (recovery) rates of patients at 24 months of transplantation ($n = 21$, 70%) are presented in Fig. 4A. The immune recovery mostly occurred in CD3$^+$ T-cell, followed by CD4$^+$ T and CD19$^+$ B cells, with the highest values noted in classical SCID as compared to AS patients (Fig. S1A-C). CD3$^+$ T-cell reconstitution was eventually achieved in 19 patients (90.5%). When the 6th, 12th, and 24th months reconstitution rates of the patients were evaluated, gradually increasing curves were observed in counts and percentages as 70%, 76.5%, and 90.5%, respectively (Fig. 4B).

CD4$^+$ T-cell reconstitution rate beyond the 12 months post-transplantation time point was observed in 15 (71.4%) patients. When the lymphocyte subsets of the patients at the last follow-up were examined, CD4$^+$ T-cell reconstitution was observed in all patients with non-*RAG* mutation ($n = 8$, 100%), which was higher than in *RAG*-mutant patients ($p = 0.035$) (Fig. 4C and Fig. S2A). Interestingly, CD4$^+$ T-cell reconstitution was superior in patients who were transplanted from peripheral blood stem cell sources ($n = 7$, 100%) compared to other sources ($p = 0.044$) (Fig. S2B). Furthermore, ten out of 11 (90.9%) gender-matched

Table 2 The donor types, sources, and conditioning regimens of HSCT

Patient	Subgroup	Genetic defect	Diagnostic age (month)	Donor type	Stem cell source	Conditioning	Outcome
P11	SCID	Undetermined	4	MSD	BM	No	Alive
P12	SCID	*ADA*	6	MRD	PBSC	MAC (Bu12 + Flu)	Alive
P13	SCID	Undetermined	5	MMRD	PBSC	No	Deceased at 2.5 months of HSCT
P14	SCID	Undetermined	1	MMRD	PBSC	No	Deceased at 4 months of HSCT
P15	SCID	Undetermined	0	MUD	UCB	MAC (Bu12 + Flu)	Alive
P16	SCID	*ADA*	2	MRD	BM	No	Alive
P17	SCID	*ADA*	0	MRD	BM	No	Deceased at 4 months of HSCT
P19	SCID	*DCLRE1C*	4	MUD	UCB	MAC (Bu16 + Flu)	Deceased at 4 months of HSCT
P20	SCID	Undetermined	0	MMRD	BM	No	Alive
P22	SCID	Undetermined	4	MSD	BM	No	Alive
P23	SCID	Undetermined	3	MRD	BM	No	Alive
P24	SCID	*IL7Ra*	3	MUD	PBSC	MAC (Bu12 + Flu)	Alive
P25	SCID	*PNP*	15	MRD	BM	MAC (Bu19.2 + Flu)	Alive
P26	SCID	*DCLRE1C*	3.5	MMRD	BM	RTC (Tre10 + Flu)	Alive
P27	SCID	Undetermined	4	MSD	BM	RIC (CY + Flu)	Alive
P28	SCID	Undetermined	3	MRD	BM	No	Alive
P31	Omenn	*RAG2*	3	MSD	BM	No	Alive
P32	Omenn	Undetermined	2	MSD	BM	MAC (Bu16 + Flu)	Deceased at 3 months of HSCT
P33	Omenn	*RAG2*	4	MSD	BM	MAC (Bu16 + Flu)	Alive
P34	Omenn	*RAG1*	1	MMRD	BM	RTC (Tre10 + Flu)	Alive
P43	AS	*ADA*	10	MSD	BM	MAC (Bu16 + Flu)	Alive
P44	AS	*DCLRE1C*	63	MUD	PBSC	MAC (Bu12 + Flu)	Alive
P45	AS	*RAG1*	42	MUD	BM	MAC (Bu12 + Flu)	Alive
P46	AS	*RAG2*	46	MUD	BM	MAC (Bu12 + Flu)	Alive
P47	AS	*ADA*	15	MSD	BM	No	Alive
P48	AS	*RAG1*	44	MMRD	BM	RTC (Tre14 + Flu)	Alive
P49	AS	*RAG2*	70	MUD	PBSC	RTC (Tre14 + Flu)	Alive
P50	AS	Undetermined	4	MRD	PBSC	RTC (Tre10 + Flu)	Alive
P51	AS	Undetermined	11	MSD	BM	No	Alive
P54	AS	*NHEJ1*	24	MUD	UCB	RIC (CY + Flu)	Alive

ADA, adenosine deaminase; *BM*, bone marrow; *DCLRE1C*, DNA cross-link repair 1C; *IL7R*, interleukin 7 receptor; *MRD*, matched related donor; *MSD*, matched sibling donor; *MUD*, matched unrelated donor; *NHEJ1*, non-homologous end-joining factor 1; *PBSC*, peripheral blood stem cell; *PNP*, purine nucleoside phosphorylase; *RAG*, recombination activating gene; *RIC*, reduced intensity conditioning; *MAC*, myeloablative conditioning; *RTC*, reduced toxicity conditioning; *UCB*, umbilical cord blood. *Bu*, busulfan; *Tre*, treosulfan; *Flu*, fludarabine; *CY*, cyclophosphamide

Cumulative doses of busulfan and treosulfan are shown in the table. Total prescribed cumulative doses of busulfan and treosulfan are reported as mg/kg and mg/m^2, respectively

transplantations from HLA-identical and non-identical donors trended toward better CD4$^+$ T-cell recovery than in non-gender-matched donors ($n=5$, $p=0.063$). The 6th, 12th, and 24th months recovery rates gradually increased as 62%, 58%, and 71.4%, respectively (Fig. 4B). The t-SNE analysis of T-cell subsets according to the CD4$^+$ T-cell recovery rates revealed better normalized cellular profiles, especially in the naïve T cell compartment, after transplantation in patients with high CD4$^+$ T cells (Fig. S3A and B). Factors including receiving conditioning or GvHD prophylaxis, transplantation from HLA-matched donors, GvHD, and CMV reactivation were all not associated with CD4$^+$ T cell reconstitution.

B-cell reconstitution beyond the 12 months post-transplantation time point was achieved in 13 patients (61.9%). Eleven out of 12 (91.7%) gender-matched HLA-identical or non-identical transplantations achieved adequate recovery compared to non-gender-matched donors ($n=2$, $p=0.002$) (Fig. S4A). Furthermore, and similar to CD4$^+$ T-cell recovery, peripheral blood stem cell sources provided a higher rate of B-cell reconstitution after HSCT ($p=0.028$) (Fig. S4B). When tissue HLA compatibility and B-cell reconstitution were evaluated, 13 (68.4%) of the HLA-compatible transplants trended toward a superior rate of B-cell recovery compared to the others ($p = 0.055$, Fig. 4D). Interestingly, B-cell reconstitution was not observed in any of the patients with haploidentical transplantation. In total, nine (90%) of ten patients who received a conditioning regimen achieved better B-cell reconstitution rate ($p = 0.003$, Fig. 4D) and the general recovery rate gradually increased over time (6th, 12th, and 24th months recovery rates: 42%, 47.6%, and 60%, respectively, Fig. 4B). At the last follow-up evaluation (median 25 months), switched memory B-cell formation was detected in 84.6% of patients and only three patients (P20, P22, P28) were still on IgRT. Infection during transplantation, genotype, CMV reactivation, and experience of GvHD did not affect B-cell reconstitution.

Analysis of Factors Influencing Chimerism

Post-transplant whole blood total chimerism rates of the patients were evaluated at the 1st, 3rd, 6th, and 12th months, and during the final follow-up visits. The chimerism showed steady percentages with a mean of 74.5 ± 33.2 at last visit evaluation (Fig. 5A). The rates of chimerism were not different among the patients' group ($p > 0.05$). Conditioning regimens provided higher chimerism rates compared to non-conditioning transplantations, especially with MAC ($p = 0.001$, Fig. 5B). Other major factors related to better chimerism rates were gender-matched HLA-identical or non-identical transplantations ($p = 0.025$), peripheral blood stem cell source ($p = 0.003$), and non-*RAG* genotypes ($p = 0.039$). Patients with low chimerism showed enough disease control and did not require interventions (lymphocyte infusion or re-transplantation) during the follow-up.

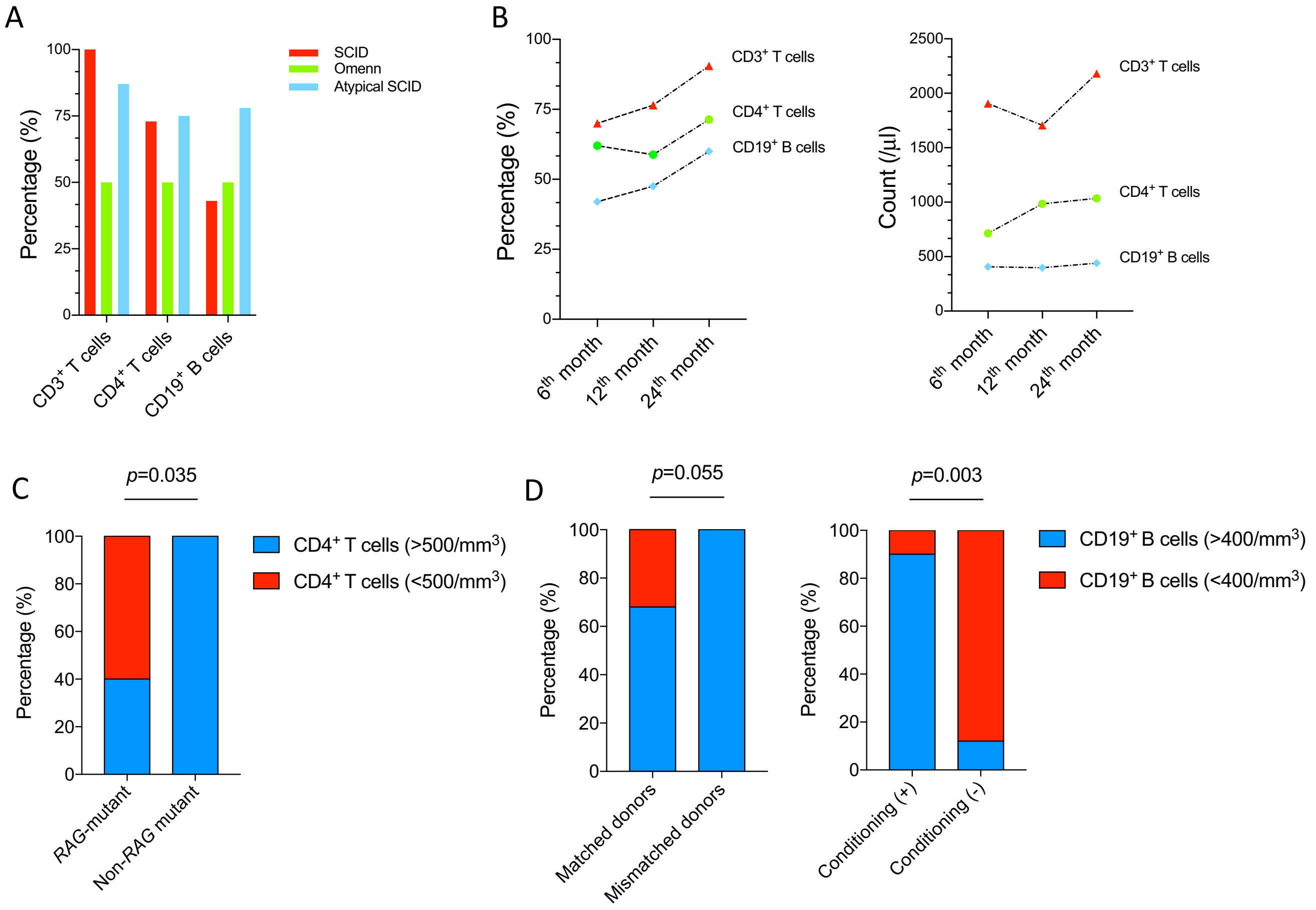

Fig. 4 The immune recovery mostly observed in the CD3$^+$ T cells with the highest values in SCID patients. **A** The percentage rates of immune recovery among groups. **B** The percentage rates and absolute count numbers of recovery over time. **C** CD4$^+$ T cells recovery ratio according to the genotype. **D** CD19$^+$ B cells recovery ratio according to donor types and conditioning used during transplantation. The T- and B-cell recoveries were defined as CD3$^+$ T-cell (> 1000/mm^3), CD4$^+$ T-cell (> 500/mm^3), and CD19$^+$ B-cell (> 400/mm^3) with detectible serum IgA level and independence from immunoglobulin replacement therapy. Fisher's exact test was used for comparisons

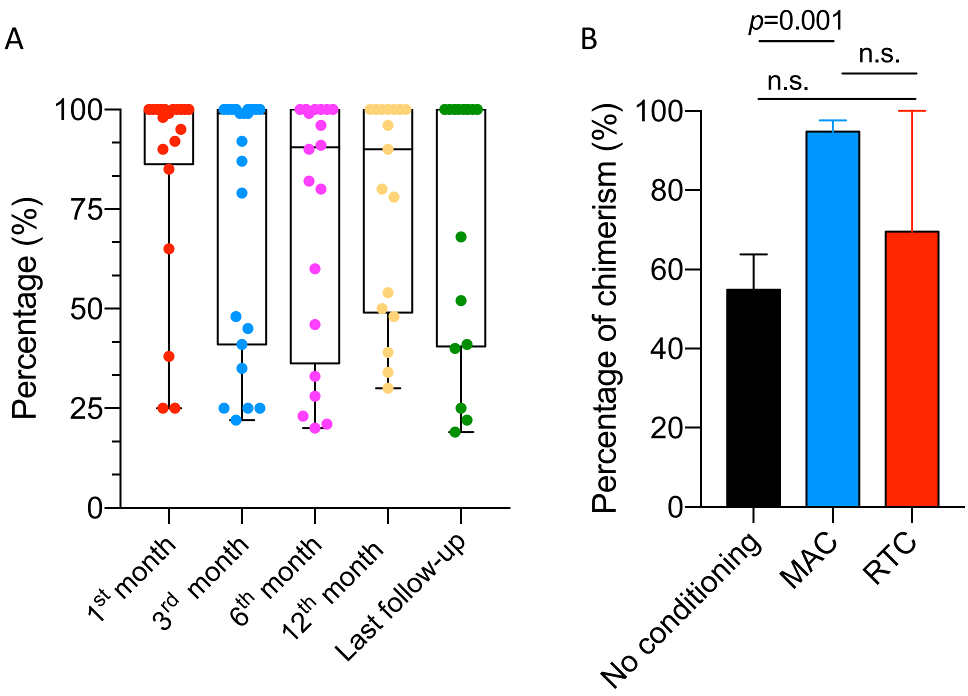

Fig. 5 Steady total donor chimerism after transplantation and higher levels with conditioning. **A** The whole blood total chimerism rate over time is expressed as percentages. **B** Percentage of chimerism in terms of conditioning regimens. Mann–Whitney *U* test was used for comparisons. MAC, myeloablative conditioning; RTC, reduced toxicity conditioning

Survival Rate After HSCT and Factors Affecting the Outcome

The OS probability after transplantation was 82.1 ± 7.0%, significantly better than non-transplanted patients ($p = 0.001$, Fig. 6A), and was not different neither among three SCID groups nor according to immunophenotyping (Fig. 6B). All the *RAG*-mutant patients were alive after transplantation, while non-*RAG* patients showed an 83.3% survival rate, and there was no statistical difference in terms of OS between two groups ($p > 0.05$). The major negative factors interfering with survival rates were infections at transplantation and mismatched donor sources ($p = 0.030$ and $p = 0.015$; respectively, Fig. 6C and D). Cox regression analysis revealed 14.5- and 15.6-times higher mortality rates in terms of infections at HSCT and donor mismatched condition ($p = 0.040$, $p = 0.020$; respectively). Female donor into male recipient, donor CMV positivity, donor stem cell sources, and receiving conditioning did not influence the OS ($p > 0.05$).

TCR Vβ Repertoire Changing After Transplantation

Since post-transplantation TCR diversity is important for event-free survival, we investigated variable regions of the receptor by flow cytometry in 20 transplanted patients (15). In general, the Vβ repertoire of $CD4^+$ and $CD8^+$ T cells at the 12th month of transplantation was broadly distributed similar to those of healthy controls (Fig. 7A and B), reflecting in the process a successful transplantation outcome in the evaluated patients. However, we detected that some immune reconstitution parameters were significantly associated with particular Vβ clones. The $CD3^+$ T-cell VB5.2 and $CD4^+$ T-cell VB18 clones were observed in higher frequencies in patients with a sufficient $CD4^+$ T-cell reconstitution compared to those with lower $CD4^+$ T-cell counts ($p = 0.015$, $p = 0.030$; respectively) (Fig. 7C and D). These parameters may be helpful in predicting effective $CD4^+$ T-cell reconstitution.

Discussion

By evaluating clinical and immunological parameters pre- and post-transplantation in a cohort of 54 Turkish SCID patients, we identified a number of factors influencing long-term outcomes. Successful immune recovery was influenced by the stem cell sources, patient disease genotypes, and conditioning regimens. Post-transplantation favorable outcomes were inversely associated with infections and using mismatched donors. A normal distribution of the Vβ repertoire post-transplant was associated with a favorable recovery for the T-cell compartment.

The most common immune phenotype in our SCID cohort was T-B-NK + due to *RAG1* and *RAG2* mutations. In a recent study, we detected a high consanguinity rate with T-B-SCID phenotype, explaining the distinct distribution of this disease in our geographical area [19]. Previously it has been demonstrated that *RAG* mutations are a more common cause of SCID than those targeting *IL2RG* in countries with

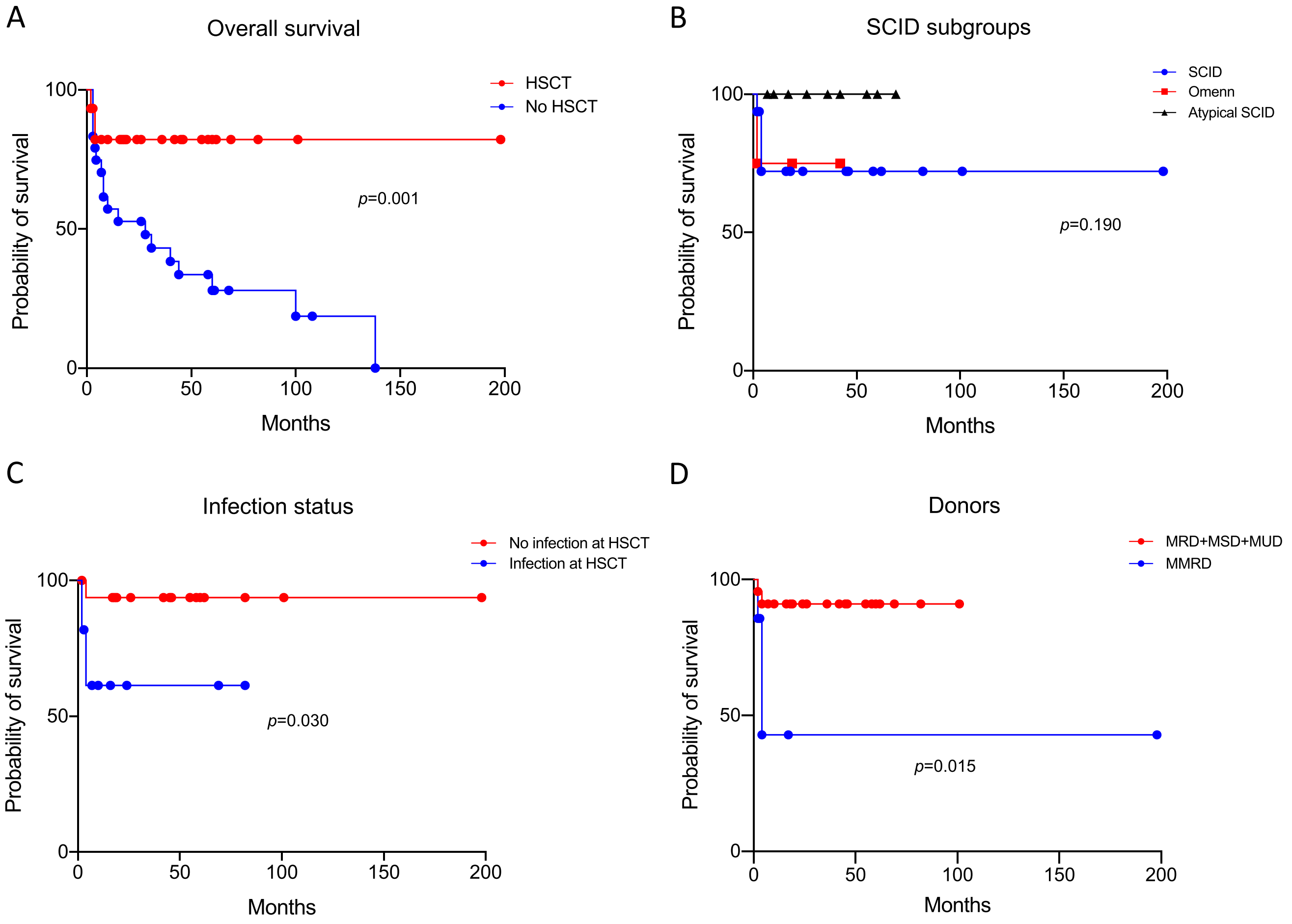

Fig. 6 Kaplan–Meier survival curves of SCID patients. Kaplan–Meier survival curves demonstrating overall survival with/without HSCT (**A**), survival analysis after transplantation comparing subgroups of SCID (**B**), with/without infections (**C**), and matched/mismatched donors (**D**). HSCT, hematopoietic stem cell transplantation

high consanguinity [20, 21]. Another notable finding in our cohort was the late age at diagnosis (mean: 5.2 months) with high rates of lung infections (79.6%) and CMV positivity (55.6%) during admission, factors that are known as negative predictors of favorable prognosis [4, 9, 10, 14]. We also found that atypical SCID patients presented at an older age, had frequent autoimmune manifestations, mainly characterized by hematological autoimmunities, and were delayed in undergoing transplantation compared to patients with other forms of the disease. Our findings of delayed diagnosis in AS patients are similar to those reported by other groups [7, 22]. More generally, our results confirm the delay of diagnosis and treatment of SCID patients in Turkey. These findings thus emphasize the need to implement a national neonatal SCID screening program, which would enable early diagnosis and intervention, and accordingly favor improved outcomes [23].

Molecular defects are known to affect the success of transplantation [8, 24, 25]. In general, B(+) SCIDs display better survival after transplantation compared to the B(−) ones. Among the SCID patients, those with *IL2RG*, *JAK3*, *IL7R*, and *RAG1/2* mutations usually have better outcomes than those with *DCLRE1C* mutations [8]. In a similar vein, autoimmune and inflammatory events and GvHD were observed more frequently in SCID patients with *DCLRE1C* mutations [25]. In our study, due to the limited number of patients, we did not analyze the effect of genotypes on survival. However, we detected better CD4^{+} T reconstitution and chimerism rates in patients with non-*RAG* genotype compared to *RAG* genotyped patients. Nevertheless, in SCID patients, post-transplant donor chimerism of 5–10% would be enough to control the disease manifestations, which is usually independent of the genetic background [26].

In our study, the survival rate after HLA-compatible transplantation was 91%. One of the most important factors affecting survival is the donor source [4, 8]. A previous long-term follow-up study on SCID patients post-transplantation revealed 85% survival with HLA-compatible transplantations, and was highest in matched sibling donors [27]. The conditioning regimens given during HSCT are another

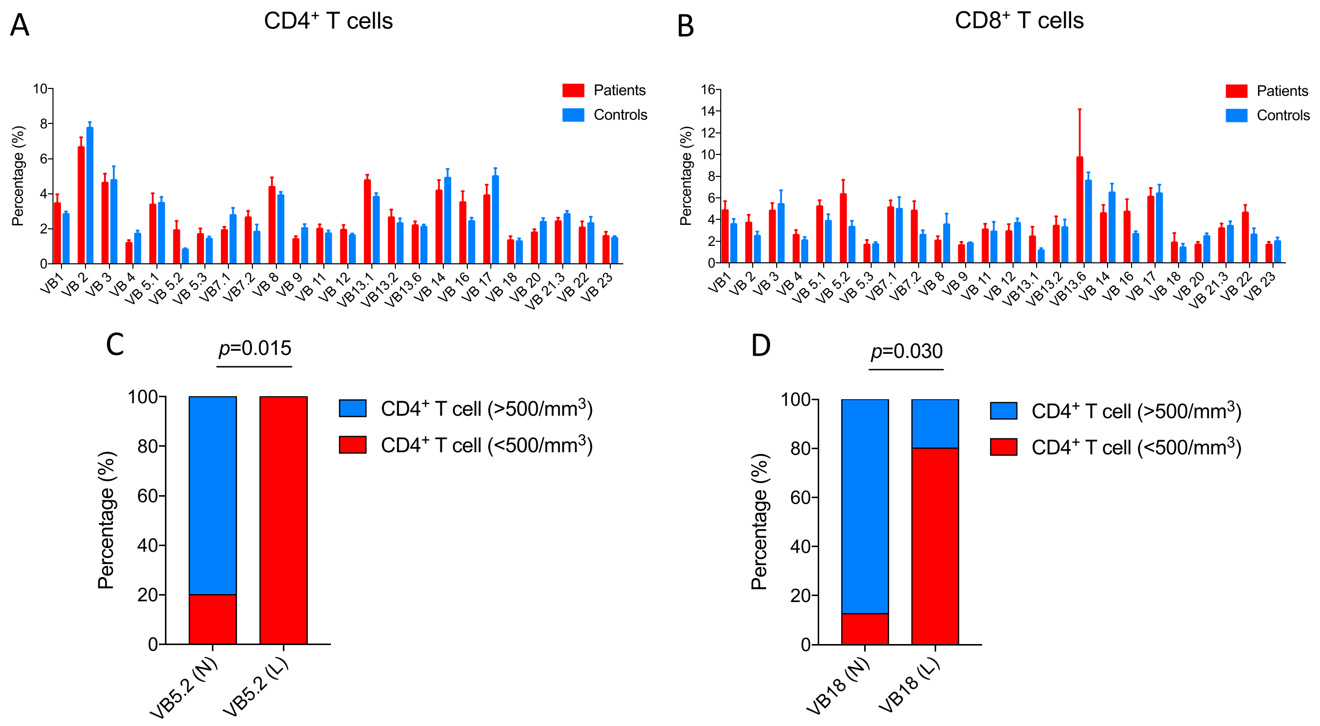

Fig. 7 Sufficient Vβ repertoire in CD4$^+$, and CD8$^+$ T cells after transplantation. The bar graphs of Vβ repertoire in CD4$^+$ T cells (**A**) and CD8$^+$ T cells (**B**) of 20 transplanted patients. The rate of formation of VB5.2 (**C**) and VB18 (**D**) clones after CD4$^+$ T cell reconstitution. N, normal; L, low

variable in SCID therapy, and the choice of a particular regimen is influenced by the SCID phenotype and genotype, as well as by the availability of donor types [10, 11, 28]. In the study conducted by Haddad et al., conditioning regimens provided better T- and B-cell recoveries with no effect on survival [8]. Our results are compatible with the results of Haddad et al. in revealing further B-cell reconstitution and independence of IgRT in those patients receiving a conditioning regimen but without influencing the survival rate [29]. It is worth mentioning that apart from the mutation genotype, the clinical condition of the patient would be the major determining factor in choosing a conditioning regimen among those available. In case of life-threatening infections, non-conditioning or RIC regimens would provide better engraftment with minimal toxicity [28].

Higher total or mixed type lymphoid chimerism with better myeloid chimerism can be achieved in IEI patients when peripheral blood stem cell sources with a fludarabine and melphalan conditioning regimen were used for transplantation from matched donors. However, this combination did not result in a better OS [30]. Frequently, a bone marrow stem cell source with a myeloablative regimen is preferred for pediatric transplantation to decrease the high rate of GvHD [31]. The higher rates of T- and B-cell recovery and increased chimerism in our study when using peripheral stem cell sources argue for using this approach in IEI patients especially for matched donors, which would not increase the risk for GvHD. Further studies are warranted to demonstrate the effect of stem cell sources on patients' survival.

An essential step for successful transplantation is the development of a broad TCR repertoire [15, 32]. We found polyclonal TCR diversity after transplantation in all of the tested patients. Interestingly, our results demonstrated skewing to some clones, which were associated with an adequate CD4$^+$ T reconstitution rate. A high ratio of VB18 and VB5.2 clones may be helpful in predicting and closely monitoring early CD4$^+$ T reconstitution and in implementing an early intervention to rescue a faltering graft after HSCT. However, further studies will be required to validate this prediction.

In conclusion, the clinical and laboratory markers of disease outcome identified in our study may prove useful in enabling early SCID diagnosis and in predicting prognosis. Comparative studies on the different forms of SCID may also provide a better understanding of the long-term natural course of these subgroups. Finally, determining the pre- and post-transplant factors influencing patient outcomes can be useful in guiding physicians to provide early corrective therapeutic interventions to improve immune reconstitution post-transplant.

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Author Contribution S.B. and E.O. conceptualized and supervised the study. D.B., M.C.C., A.B., G.A., and Y.C. performed the experiments. A.K., S.B.E, N.K., E.N., A.P.S., R.B., A.O., E.K.A., and S.B. provided patient care and collected samples and clinical data. K.Y., S.K., G.T.K., and A.Y. performed transplantation of the patients. S.B. and E.O. wrote the paper. All authors reviewed and approved the final version of the manuscript.

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Data Availability The data generated during the study are included in this published article and its supplementary file.

Code Availability Not applicable.

Declarations

Ethics Approval The study was approved by the Ethics Committee of Marmara University, School of Medicine (09.2019.511).

Consent to Participate Informed consent for participation was obtained from all individuals.

Consent for Publication Informed publication consent was obtained from all participants.

Conflict of Interest The authors declare no competing interests.

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