Hematopoietic cell transplantation in severe combined immunodeficiency: The SCETIDE 2006-2014 European cohort

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Arjan C. Lankester, MD, PhD,[a] Benedicte Neven, MD, PhD,[b,c,d] Nizar Mahlaoui, MD, PhD,[e] Erik G. J. von Asmuth, MD,[a] Virginie Courteille,[e] Mikael Alligon,[e] Michael H. Albert, MD, PhD,[f] Isabelle Badell Serra, MD,[g] Peter Bader, MD, PhD,[h] Dmitry Balashov, MD,[i] Rita Beier, MD,[j] Yves Bertrand, MD, PhD,[k] Stephane Blanche, MD, PhD,[b] Victoria Bordon, MD, PhD,[l] Robbert G. Bredius, MD, PhD,[a] Andrew Cant, MD,[m] Marina Cavazzana, MD, PhD,[c,n,o,p] Cristina Diaz-de-Heredia, MD,[q] Figen Dogu, MD,[r] Karoline Ehlert, MD,[s,t] Natacha Entz-Werle, MD, PhD,[u] Anders Fasth, MD, PhD,[v] Francesca Ferrua, MD, PhD,[w] Alina Ferster, MD,[x] Renata Formankova, MD, PhD,[y] Wilhelm Friedrich, MD, PhD,[z] Marta Gonzalez-Vicent, MD, PhD,[aa] Jolanta Gozdzik, MD, PhD,[bb] Tayfun Güngör, MD, PhD,[cc] Manfred Hoenig, MD, PhD,[z] Aydan Ikinciogullari, MD,[r] Krzysztof Kalwak, MD, PhD,[dd] Savas Kansoy, MD, PhD,[ee] Alphan Kupesiz, MD, PhD,[ff] Arnalda Lanfranchi, MD,[gg] Caroline A. Lindemans, MD, PhD,[hh,ii] Roland Meisel, MD, PhD,[jj] Gerard Michel, MD, PhD,[kk] Nuno A. A. Miranda, MD,[ll] Jose Moraleda, MD, PhD,[mm] Despina Moshous, MD, PhD,[b,c,p] Herbert Pichler, MD,[nn] Kanchan Rao, MD,[oo] Petr Sedlacek, MD, PhD,[y] Mary Slatter, MD, PhD,[m] Elena Soncini, MD,[pp] Carsten Speckmann, MD,[qq] Mikael Sundin, MD, PhD,[rr] Amos Toren, MD, PhD,[ss] Kim Vettenranta, MD, PhD,[tt] Austen Worth, MD, PhD,[oo] Mehmet A. Yeşilipek, MD, PhD,[uu] Marco Zecca, MD,[vv] Fulvio Porta, MD,[pp] Ansgar Schulz, MD, PhD,[z] Paul Veys, MD,[oo] Alain Fischer, MD, PhD,[b,c] and Andrew R. Gennery, MD, PhD[m]

Leiden and Utrecht, The Netherlands; Paris, Lyon, Strasbourg, and Marseille, France; Munich, Frankfurt, Hannover, Münster, Greifswald, Ulm, Düsseldorf, and Freiburg, Germany; Barcelona, Madrid, and Murcia, Spain; Moscow, Russia; Ghent, Belgium; Newcastle upon Tyne and London, United Kingdom; Ankara, Izmir, and Antalya, Turkey; Gothenburg, Sweden; Milan, Brescia, and Pavia, Italy; Brussels, Belgium; Prague, Czech Republic; Krakow and Wroclaw, Poland; Zurich, Switzerland; Lisbon, Portugal; Vienna, Austria; Stockholm, Sweden; Tel-Hashomer, Israel; and Helsinki, Finland

Background: Hematopoietic stem cell transplantation (HSCT) represents a curative treatment for patients with severe combined immunodeficiency (SCID), a group of monogenic immune disorders with an otherwise fatal outcome.

Objective: We performed a comprehensive multicenter analysis of genotype-specific HSCT outcome, including detailed analysis of immune reconstitution (IR) and the predictive value for clinical outcome.

From [a]the Pediatric Stem Cell Transplantation Program and Laboratory for Pediatric Immunology, Willem-Alexander Children's Hospital, Leiden University Medical Center, Leiden; [b]the Unité d'Immuno-hematologie et Rhumatologie Pédiatrique, Hôpital Universitaire Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France; [c]the Université de Paris, Paris; [d]the Institut Imagine, INSERM UMR1163, Laboratory of Immunogenetics of Pediatric Autoimmune Diseases, Paris; [e]the French National Reference Center for Primary Immunodeficiencies (CEREDIH) and European Registry for Stem Cell Transplantation for Primary Immunodeficiencies (SCETIDE), Hôpital Universitaire Necker-Enfants malades, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris; [f]Dr von Haunersches University Children's Hospital, Munich; [g]the Hospital Clínic, Sant Creu i Sant Pau Hospital, Bone Marrow Transplantation Unit, Barcelona; [h]the Department for Children and Adolescents Medicine, Division for Stem Cell Transplantation and Immunology, University Hospital Frankfurt, Frankfurt; [i]the Department for Hematopoietic Stem Cell Transplantation, Dmitriy Rogachev National Center for Pediatric Hematology, Oncology and Immunology, Moscow; [j]the Klinik für Pädiatrische Hämatologie und Onkologie, Hannover Medical School, Hannover; [k]the Institut d'Hématologie et d'Oncologie Pédiatrique, Hospices Civils de Lyon and Université Claude Bernard Lyon 1, Lyon; [l]the Department of Pediatric Hemato-oncology and Stem Cell Transplant, Ghent University Hospital, Ghent; [m]the Translational and Clinical Research Institute, Newcastle University, and the Paediatric Haematopoietic Stem Cell Transplant Unit, Great North Children's Hospital, Newcastle upon Tyne; [n]the Paris Biotherapy Department, Necker Children's Hospital Assistance, and [o]the Biotherapy Clinical Investigation Center, Assistance Publique Hopitaux de Paris, INSERM, Paris; [p]the Laboratory of Genomic Dynamics in the Immune System, Institut Imagine, INSERM UMR1163, Paris; [q]the Department of Pediatric Oncology and Hematology, and Hematopoietic Stem Cell Transplantation, Hospital Universitario Vall d'Hebron, Barcelona; [r]the Department of PIA and the BMT Unit, Ankara University, Ankara; [s]the Department of Pediatric Hematology and Oncology, Universitätsklinikum Münster, Münster; [t]the Department of Pediatric Hematology and Oncology, University of Greifswald, Greifswald; [u]the Pediatric Onco-hematology Department–Pediatrics III, University Hospital of Strasbourg, Strasbourg; [v]the Department of Pediatrics, Institute of Clinical Sciences, University of Gothenburg, Gothenburg; [w]the Pediatric Immunohematology and Bone Marrow Transplantation Unit and the San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), IRCCS San Raffaele Scientific Institute, Milan; [x]the Department of Hemato-oncology, Hôpital Universitaire des Enfants Reine Fabiola, Brussels; [y]the Department of Pediatric Hematology and Oncology, Teaching Hospital Motol, 2nd Medical School, Charles University Motol, Prague; [z]the Department of Pediatrics, University Medical Center Ulm, Ulm; [aa]the Hematopoietic Stem Cell Transplantation and Cellular Therapy Unit, Hospital Infantil Universitario "Niño Jesus," Madrid; [bb]the Department of Clinical Immunology and Transplantation, Jagiellonian University Medical College, Krakow; [cc]the Department of Hematology, Oncology, Immunology, Gene Therapy and Stem Cell Transplantation, and Children's Research Center (CRC), University Children's Hospital, Zurich; [dd]the Department of Pediatric Hematology, Oncology, and BMT, Wroclaw Medical University, Wroclaw; [ee]the Department of Pediatric Hematology and Oncology, Ege University Hospital, Izmir; [ff]the Department of Pediatrics, Hematology, and Oncology, Akdeniz University School of Medicine, Antalya; [gg]the Diagnostic Department, Stem Cell Laboratory, Section of Hematology and Blood Coagulation, Clinical Chemistry Laboratory, ASST Spedali Civili, Brescia; [hh]the Department of Stem Cell Transplantation, Princess Maxima Center for Pediatric Oncology, Utrecht; [ii]the Department of Pediatrics, University Medical Center Utrecht, University of Utrecht, Utrecht; [jj]the Department of Pediatric Oncology, Hematology,

Methods: HSCT outcome was studied in 338 patients with genetically confirmed SCID who underwent transplantation in 2006-2014 and who were registered in the SCETIDE registry. In a representative subgroup of 152 patients, data on IR and long-term clinical outcome were analyzed.

Results: Two-year OS was similar with matched family and unrelated donors and better than mismatched donor HSCT ($P < .001$). The 2-year event-free survival (EFS) was similar in matched and mismatched unrelated donor and less favorable in mismatched related donor (MMRD) HSCT ($P < .001$). Genetic subgroups did not differ in 2-year OS ($P = .1$) and EFS ($P = .073$). In multivariate analysis, pretransplantation infections and use of MMRDs were associated with less favorable OS and EFS. With a median follow-up of 6.2 years (range, 2.0-11.8 years), 73 of 152 patients in the IR cohort were alive and well without Ig dependency. IL-2 receptor gamma chain/Janus kinase 3/IL-7 receptor–deficient SCID, myeloablative conditioning, matched donor HSCT, and naive CD4 T lymphocytes >0.5 × 10^{e3}/μL at +1 year were identified as independent predictors of favorable clinical and immunologic outcome.

Conclusion: Recent advances in HSCT in SCID patients have resulted in improved OS and EFS in all genotypes and donor types. To achieve a favorable long-term outcome, treatment strategies should aim for optimal naive CD4 T lymphocyte regeneration. (J Allergy Clin Immunol 2022;149:1744-54.)

Key words: *SCID, genetic subgroups, conditioning, pretransplantation infections, immune reconstitution*

Abbreviations used

ADA: Adenosine deaminase
BM: Bone marrow
CI: Confidence interval
EFS: Event-free survival
GvHD: Graft-versus-host disease
HSCT: Hematopoietic stem cell transplantation
IL2Rγ: IL-2 receptor gamma chain
IL7R: IL-7 receptor
IR: Immune reconstitution
JAK3: Janus kinase 3
MAC: Myeloablative conditioning
(M)MD: (Mis)matched donor
(M)MRD: (Mis)matched related donor
(M)MUD: (Mis)matched unrelated donor
MSD: Matched sibling donor
OS: Overall survival
RAG: Recombinase activating gene
SCETIDE: Stem Cell Transplant in Primary Immune Deficiency in Europe
SCID: Severe combined immunodeficiency

Severe combined immunodeficiency (SCID) is a group of inherited conditions typically defined by lack of T lymphocytes resulting from an intrinsic T lymphocyte differentiation defect associated or not with lack of B lymphocyte and/or natural killer cell differentiation, depending on the underlying monogenic defect.[1] Untreated, SCID is usually fatal in the first year of life as a result of life-threatening infections. Five decades ago, the curative potential of allogeneic hematopoietic stem cell transplantation (HSCT) was first demonstrated in SCID patients,[2,3] and since then, the Stem Cell Transplant in Primary Immune Deficiency in Europe (SCETIDE) registry has collected data on more than 1500 transplanted SCID patients. Survival of transplanted SCID patients has improved over time, mostly as a result of our better understanding of the biology of SCID, improvements in supportive care, advances in HLA typing technology, expanded donor sources, optimization of conditioning regimens, and graft manipulation to limit transplant-related toxicity and prevent graft-versus-host disease (GvHD).[4-8] In that context, the quality of survival from a clinical and immunologic perspective has become increasingly important. Previous single-center and multicenter reports have pointed to the effect of SCID type, donor type, and conditioning on overall survival (OS), immune reconstitution (IR), and clinical outcome.[7,9-11]

We here report the transplant outcome in a cohort of 338 genetically defined SCID patients transplanted in European centers between 2006 and 2014 as registered in the SCETIDE database. The availability of HLA high-resolution DNA typing data plus a genetic diagnosis in all patients for the first time permitted comprehensive subgroup analysis. In addition, detailed longitudinal IR and clinical outcome data were studied in a representative subgroup of 152 SCID patients.

and Clinical Immunology, Medical Faculty, Division of Pediatric Stem Cell Therapy, Heinrich-Heine-University, Düsseldorf; [kk]the Service d'Hématologie Immunologie Oncologie Pédiatrique, CHU La Timone, Marseille; [ll]the BMT Unit, Instituto Português de Oncologia de Lisboa, Lisbon; [mm]the Department of Hematology and Hemotherapy, Hospital Virgen de la Arrixaca-IMIB, Murcia; [nn]the Department of Stem Cell Transplantation, Children's Cancer Institute, St Anna Hospital, Vienna; [oo]the Great Ormond Street (GOS) Hospital for Children NHS Foundation Trust and University College London GOS Institute of Child Health, London; [pp]the Pediatric Oncohaematology and BMT Unit, Children's Hospital Brescia, Brescia; [qq]the Department of Pediatric Hematology and Oncology, Center for Pediatrics and Adolescent Medicine, and Institute for Immunodeficiency, Center for Chronic Immunodeficiency (CCI), Faculty of Medicine, Medical Center, University of Freiburg, Freiburg; [rr]the Section of Pediatric Hematology, Immunology, and HCT, Astrid Lindgren Children's Hospital, Karolinska University Hospital, and Division of Pediatrics, CLINTEC, Karolinska Institutet, Stockholm; [ss]Paediatric Hemato-oncology and BMT, Sheba Medical Center, Tel-Hashomer; [tt]the University of Helsinki and Children's Hospital, University of Helsinki, Helsinki; [uu]the Pediatric Hematology, Oncology, and Pediatric Stem Cell Transplantation Unit, Medicalpark Antalya & Göztepe Hospitals, Antalya; and [vv]Pediatric Hematology/Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia.

The first 2 authors contributed equally to this article, and both should be considered first author. The last 2 authors contributed equally to this article, and both should be considered senior author.

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Corresponding author: Arjan C. Lankester, MD, PhD, Willem-Alexander Children's Hospital, Pediatric Stem Cell Transplantation Program and Laboratory for Pediatric Immunology, Leiden University Medical Center, Albinusdreef 2, 2300RC, Leiden, The Netherlands. E-mail: a.lankester@lumc.nl.

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METHODS

Study population

The study population consisted of 338 genetically defined SCID patients who received transplants between 2006 and 2014, and whose cases were reported to the SCETIDE registry. This cohort of 338 patients represented 79% of the overall group of 429 transplanted patients registered as SCID in the 2006-2014 period transplanted in 43 centers. This well-characterized and well-documented cohort was used to avoid bias by patients with atypical SCID and uncertain diagnoses. Clinical and laboratory data were collected after receipt of informed consent of the parents/caregivers. SCID patients were defined as follows: typical SCID: genetically confirmed IL-2 receptor gamma chain (IL2Rγ), Janus kinase 3 (JAK3), or IL-7 receptor deficiency, recombinase activating gene (RAG) 1, RAG2, or DCLRE1C deficiency, or adenosine deaminase (ADA) deficiency; all patients were diagnosed before the age of 1 year and received a transplant before the age of 15 months; and other SCID: patients with PNP, RMRP, ZAP70, LIG1, LIG4, XLF, AK2, and CD3 deficiency diagnosed before the age of 1 year with $CD3^+$ T lymphocytes of <300 cells/μL and received a transplant before the age of 15 months.

None of the SCID patients was diagnosed by newborn screening programs. Patients with Omenn syndrome (70 in this study period) were excluded from this study because it is a distinct entity with respect to clinical manifestations and treatment requirements.

Data and definitions

Pretransplantation active infections were defined as mycobacterial infection, symptomatic bacillus Calmette-Guérin–itis, and respiratory viral (excluding rhinovirus) and systemic viral infections. Conditioning regimens were classified as none/serotherapy only, myeloablative conditioning (MAC) with busulfan ≥8 mg/kg and treosulfan ≥30 g/m^2 total dose, mostly combined with either cyclophosphamide (200 mg/kg) or fludarabine (150 mg/m^2), and reduced-intensity conditioning using lower doses of the aforementioned chemotherapy combinations or fludarabine/melphalan. Serotherapy included anti-thymocyte globulin or alemtuzumab. Donor type and HLA matching were categorized as matched sibling donor (MSD), matched related donor (MRD), matched unrelated donor (MUD; 10/10 or 8/8 in case of unrelated donor, and 6/6 in case of cord blood), mismatched unrelated donor (MMUD), and mismatched related donor (MMRD). Stem cell sources included bone marrow (BM), mobilized peripheral blood, and umbilical cord blood. Detailed information on clinical problems and sequelae was collected with a specific questionnaire via the SCETIDE office in a representative subgroup of patients from centers with more than 10 patients transplanted over the study period with at least 2 years' follow-up (Table I). The posttransplantation events and complications used for the assessment of "alive and well" included the following: invasive/chronic infections, chronic GvHD, pulmonary disease, liver disease, renal disease, endocrine dysfunction, nutritional deficiency with support, and autoimmunity. Sequelae were defined as neurocognitive and motor impairment, growth retardation, orthopedic problems, hearing loss, and sequelae from infections that occurred before HSCT.

Immune reconstitution

Data on absolute numbers of $CD3^+/CD4^+$, $CD3^+/CD8^+$ T lymphocytes, NK cells ($CD3^-/CD16^+$ and/or $CD56^+$), naive CD4 T lymphocytes, and Ig replacement therapy were collected at +1 year, +2 years, and last follow-up (LFU) (≥3 years after stem cell transplantation). Naive CD4 T lymphocytes were defined as $CD4^+/CD45RA^+/CCR7^+$, $CD4^+/CD45RA^+/CD27^+$, or $CD4^+/CD45RA^+/CD31^+$.

Statistical analyses

We used median (minimum, maximum) to display descriptive variables for continuous quantitative variables. Survival probabilities were estimated by the Kaplan-Meier method. The log-rank test was applied to compare survival probabilities between groups. A semiparametric Cox regression model approach was used to identify independent risk factors associated with outcome after the first HSCT using stepwise backward selection. In particular, we used the Kaplan-Meier estimator to determine event-free survival (EFS), with an event defined as either a second HSCT, boost, or death. Overall survival (OS) and EFS were determined at 1, 2, and 8 years after HSCT. All *P* values were considered statistically significant when below .05. We used R 4.0.2 statistical software (https://www.r-project.org/). IR was investigated by visualizing cell counts split by diagnosis, conditioning, donor relation, and outcome; relevant categories were compared by chi-square test for categorical effects, Fisher exact test if a cell count was less than 5, and Wilcoxon-Mann-Whitney test for continuous effects. To investigate the effects of outcome on the basis of total and naive CD4 counts in a multivariate context, we used logistic regression.

RESULTS

Similar OS and EFS in different SCID genotypes

In this cohort of 338 genetically defined SCID patients (Table I), OS was 83.6% and 81.1% at 1 and 2 years, respectively, and 75.8% at LFU (median, 4.5 years; range, 0.16-11.8 years). In the major genotype specific groups, 2-year OS was 85.7% in ADA (n = 32), 87.1% in IL2Rγ (n = 87), 84.0% in JAK3 (n = 19), and 64.6% in IL-7 receptor (IL7R)-deficient SCID (n = 12), while 2-year OS in RAG1/2 (n = 53) and DCLRE1C-deficient SCID (n = 26) was 79.7% and 79.4%, respectively (not significant). The 2-year OS of the pooled IL2Rγ-JAK3-IL7R–deficient (previously known as T^-/B^+) SCID patients (83.6%; 95% confidence interval [CI], 78.0-89.7), RAG1/2- and DCLRE1C-deficient (T^-/B^-) SCID patients (79.8%; 95% CI, 72.5-87.7), ADA-deficient patients (85.7%; 95% CI, 75.8-97.0), and the minor "other" subgroup (64.3%; 95% CI, 48.7-84.7) showed no significant differences (Fig 1, *A; P* = .1). EFS in the overall cohort at 1 and 2 years and LFU was 77.6%, 74.0%, and 67.9%, respectively. In this cohort, 37 patients received a second transplant, and 14 patients received a stem cell boost. The 2-year EFS was similar in ADA-deficient (78.4%; 95% CI, 66.8-91.9), IL2Rγ-JAK3-IL7R–deficient (77.7%; 95% CI, 71.3-84.6), RAG1/2-DCLRE1C–deficient (71.4%; 95% CI, 63.4-80.5), and the group of "other" SCID (57.1%; 95% CI, 41.4-78.7) patients (Fig 1, *B; P* = .073).

Impact of donor type on overall and EFS

Two-year OS was similar with MSD (n = 64; 91.9%), MRD (n = 36; 91.7%), and MUD (n = 66; 87.9%, Fig E1, *A,* in this article's Online Repository available at www.jacionline.org). OS with these matched donors (MD) was superior to MMUD (n = 56) and MMRD (n = 116) with 2-year OS of 90.2%, 76.7%, and 70.3%, respectively; Fig 1, *C; P* < .001). However, 2-year EFS was similar with MD (2-year EFS 82.6%; 95% CI, 77.0-88.7) and MMUD (2-year EFS 75.0%; 95% CI, 64.5-87.2), while it was less favorable with MMRD (2-year EFS 61.6%; 95% CI, 53.3-71.2; Fig 1, *D; P* < .001).

Donor-related OS and EFS were analyzed in the 3 genetic subgroups. In the MD group, 2-year OS in ADA-deficient (n = 33), IL2Rγ-JAK3-IL7R–deficient (n = 70), and RAG-DCLRE1C–deficient (n = 53) SCID patients was 90.7%, 89.9%, and 92.4%, respectively (not significant). In mismatched donor (MMD) transplants in IL2Rγ-JAK3-IL7R–deficient SCID patients, a similar 2-year OS was reported for MMUD (n = 25) and MMRD (n = 60), with 80% and 78.2%, respectively (not statistically significant). In contrast, in the group of RAG-DCLRE1C–deficient patients, 2-year OS was significantly better when using MMUD (n = 17) compared to MMRD (n = 42), with 81.9% and 63.3%, respectively (*P* = .02). The number of ADA

TABLE I. Overview of 338 subjects comprising the SCID cohort

Total	SCID cohort (n = 338)	IR subcohort (n = 152)
Demographics		
Sex		
Female	113 (33)	45 (30)
Male	225 (67)	107 (70)
Age at diagnosis (years), median (min-max)	0.33 (0-1)	0.29 (0-0.75)
Age at transplantation (years), median (min-max)	0.52 (0.04-1.22)	0.48 (0.04-1.2)
Length of follow-up (years), median (min-max), excluding deaths	4.0 (0-11.8)	6.3 (2.0-11.8)
Pretransplantation infections		
Yes	138 (41)	88 (58)
No	200 (59)	64 (42)
Genetic diagnosis		
ADA	43 (13)	19 (12)
DCLRE1C	34 (10)	19 (13)
RAG1	46 (13.9)	23 (15)
RAG2	30 (9)	11 (7)
RAG (unknown)	2 (0.1)	
RAG^+DCLRE1C	112 (33)	53 (35)
IL2Rγ	109 (32)	61 (40)
JAK3	26 (8)	13 (9)
IL7R	20 (6)	6 (4)
$IL2R\gamma^+JAK3^+IL7R$	155 (46)	80 (53)
AK2	9 (2.7)	
LAT	2 (0.6)	
CD3D	2 (0.6)	
CD3E	5 (1.5)	
PNP	3 (0.9)	
LIG1	1 (0.3)	
LIG4	2 (0.6)	
XLF	1 (0.3)	
ZAP70	1 (0.3)	
CHH	2 (0.6)	
Transplantation		
Other SCID	28 (8)	
Year of transplantation		
2006	38 (11)	14 (9)
2007	41 (12)	26 (17)
2008	28 (8)	13 (9)
2009	50 (15)	21 (14)
2010	37 (11)	17 (11)
2011	35 (10)	14 (9)
2012	44 (13)	19 (13)
2013	35 (10)	12 (8)
2014	30 (9)	16 (11)
Source of hematopoietic stem cells		
BM	181 (54)	97 (64)
PBSC	89 (26)	27 (18)
BM + PBSC	2 (0.6)	2 (1)
Cord blood	66 (20)	26 (17)
Type of donor		
MSD	64 (19)	26 (17)
Matched related	36 (11)	22 (14)
Mismatched related	116 (34)	52 (34)
MUD	66 (20)	32 (21)
MMUD	56 (17)	20 (13)
Type of conditioning		
MAC	163 (49)	76 (50)
Busulfan–cyclophosphamide	30 (18)	13 (17)
Busulfan–fludarabine	40 (25)	21 (28)
Treosulfan–cyclophosphamide	16 (10)	8 (11)
Treosulfan–fludarabine	59 (36)	31 (41)
Other	18 (11)	3 (4)
Reduced-intensity conditioning	32 (10)	8 (5)
No CR/serotherapy only	137 (41)	68 (45)
Acute GvHD		
0	191 (60)	85 (59)
Grade I	39 (12)	24 (17)
Grade II	51 (16)	20 (14)
Grade III	29 (9)	11 (8)
Grade IV	7 (2)	2 (1)
Grade unknown	4 (1)	2 (1)

Data are presented as no. (%) unless otherwise indicated. *PBSC*, Peripheral blood stem cell.

patients transplanted with a MMD was too small for subgroup analysis.

In the MD group, 2-year EFS was 81.0% in ADA-deficient patients, 85.4% in IL2Rγ-JAK3-IL7R–deficient patients, and 84.4 % in RAG-DCLRE1C–deficient patients ($P = .88$). In the MMD cohort, 2-year EFS in the IL2Rγ-JAK3-IL7R–deficient group was 80.0% and 68.1% in MMUD and MMRD, respectively ($P = .29$), and in the RAG-DCLRE1C–deficient patients 76.5% and 53.6%, respectively ($P = .11$). In the overall cohort, OS and EFS were not significantly different in the 2006-2010 and 2011-2014 time periods (data not shown).

Impact of pretransplantation infections and age at transplantation on OS

Pretransplantation infections were reported in 138 patients and absent in the remaining 200 patients. They had a strong negative impact, leading to a 2-year OS of 73% (95% CI, 65.9-80.8) in infected patients compared to 86.6% (95% CI, 82.0-91.5) in noninfected patients, respectively (Fig 2, *A; P* < .001) and 2-year EFS of 65.5% (95% CI, 58.0-74.0) and 79.9% (95% CI, 74.5-85.7), respectively (Fig 2, *B; P* = .002). In contrast, age at transplantation, set at below or above 3.5 months as in previous studies,[6] was not correlated with either 2-year OS (87.8% vs 82.0%) or 2-year EFS (78.8 vs 72.2%, Fig 2, *C* and *D; P* = .15).

Impact of conditioning on OS

In the IL2Rγ-JAK3-IL7R–deficient SCID group, MAC or reduced-intensity conditioning was applied in half of the patients (73/155, 47%) whereas the majority of RAG-DCLRE1C–deficient SCID patients (85/112, 76%) received such preparative treatment. In both SCID genotype groups, patients transplanted with and without conditioning had similar survival. In the IL2Rγ-JAK3-IL7R group, 2-year OS was 84.8% versus 82.7%, and 2-year EFS 80.4% versus 75.1% (Fig 3, *A* and *B; P* = .8 and *P* = .28, respectively); in the RAG-DCLRE1C group, 2-year OS was 77.2% versus 88.0%, and 2-year EFS was 73.5% versus 65.0% (Fig 3, *C* and *D, P* = .35 and *P* = .85, respectively). Within the MAC group, the 2-year OS with fludarabine- and cyclophosphamide-containing conditioning was 89.6% and 73.8%, respectively ($P = .064$).

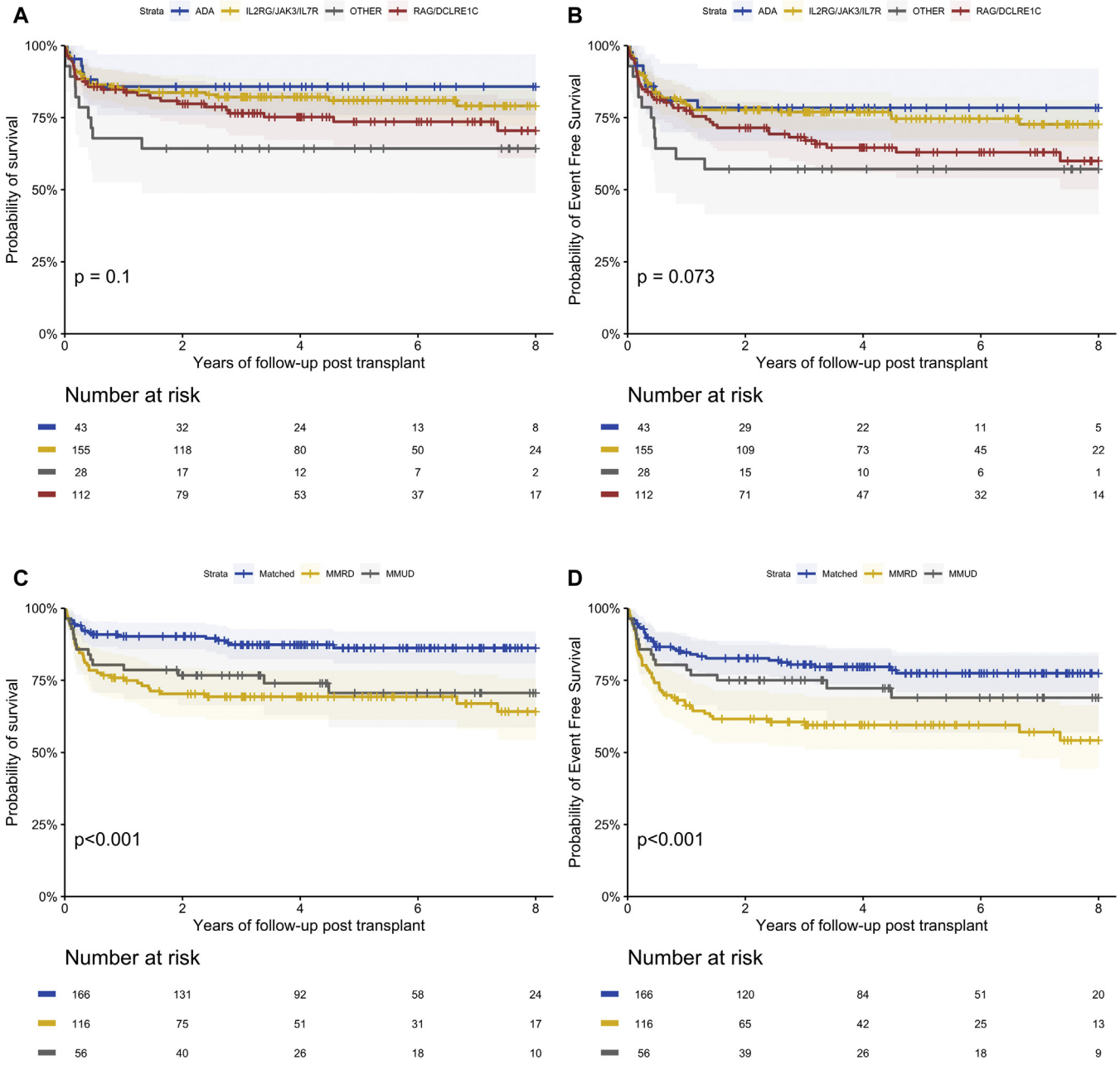

FIG 1. OS and EFS in genetic subgroups and donor types. OS (**A**) and EFS (**B**) for ADA-, IL2Rγ-JAK3-IL7R–, RAG-DCLRE1C–deficient, and "other" SCID group ($P = .1$ and $P = .073$, respectively). OS (**C**) and EFS (**D**) are shown for matched, MMUD, and MMRD groups ($P < .001$ and $P < .001$, respectively).

Impact of acute GvHD disease on OS

Data on acute GvHD were reported in 318 patients, as follows: grade 0-I, 72.6%; grade II, 16%; and grade III-IV, 11.3%. Using landmark analysis (3 months), the occurrence of severe acute GvHD (grade III-IV) was negatively correlated with survival ($P = .0031$, Fig E1, *B*); 2-year OS was 93.4% in grade 0-I, 89.5% in grade II, and 75.5% in grade III-IV patients ($P = .0052$). Acute grade II or higher GvHD occurred at the same frequency in MD (27.4%) and MMD (27.3%) transplants (not significant [$P = 1$]). Conditioning did not affect the occurrence of acute GvHD of any grade (data not shown).

Multivariate analysis on OS and EFS

In multivariate survival analysis, 2 independent factors were strongly associated with unfavorable OS and EFS: the presence of pretransplantation infections ($P < .001$ and $P < .001$, respectively) and a MMRD ($P = .006$ and $P = .003$, respectively; Table II).

Clinical outcome

Comprehensive data on long-term clinical outcome (median, 6.2 years; range, 2.0-11.8 years), and IR at 1 year and beyond were analyzed in a representative cohort of 152 SCID patients

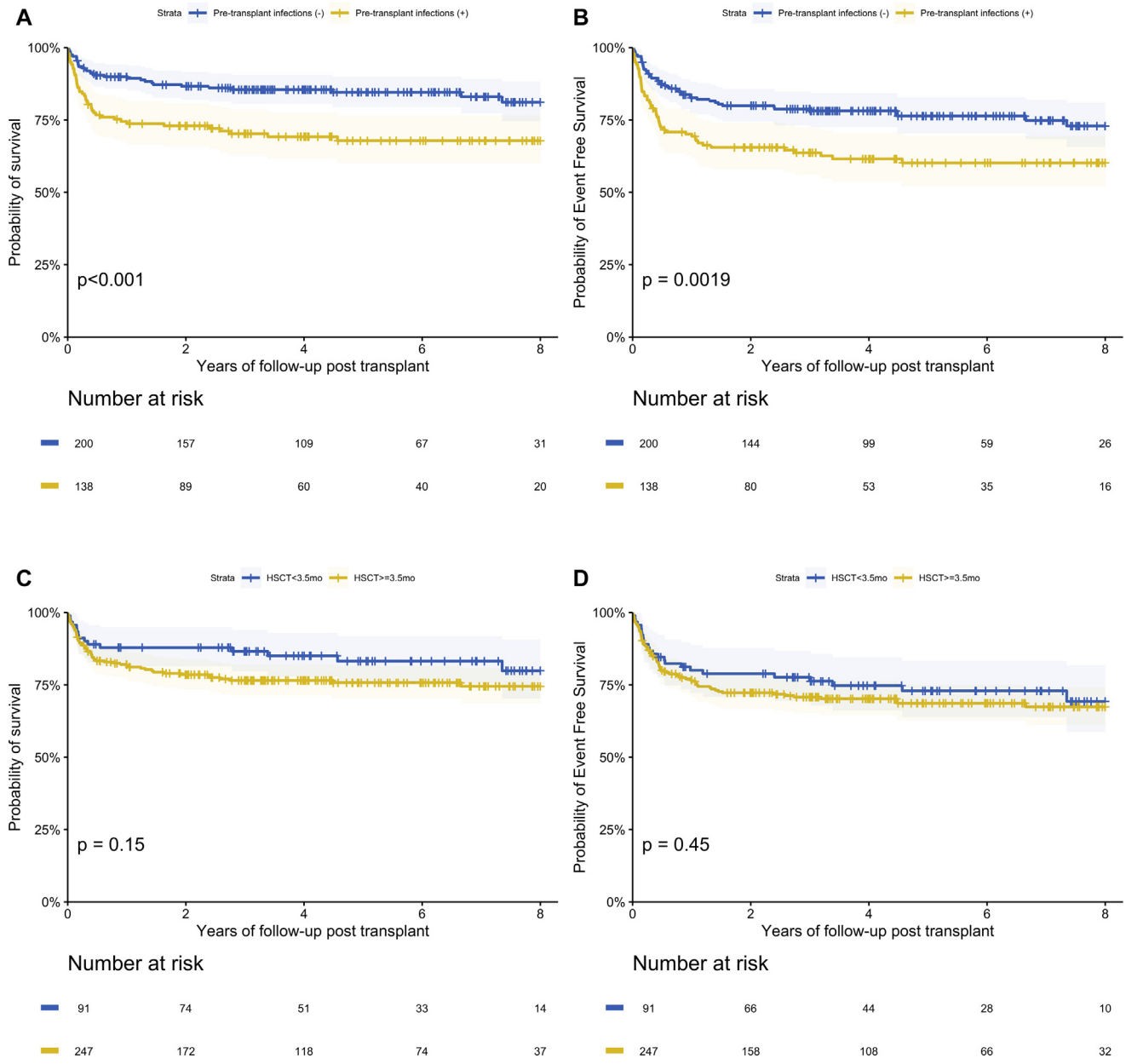

FIG 2. Impact of pretransplantation infections and age at HSCT on OS and EFS. Impact of pretransplantation infections (negative vs positive) on OS (**A**) and EFS (**B**) ($P < .001$ and $P = .002$). Impact of age at transplantation on OS (**C**) and EFS (**D**) ($P = .15$ and $P = .45$, respectively).

(Table I). Within this cohort, 93 (61.2%) of 152 patients were reported to be alive and well, of whom 73 (48%) of 152 were alive and well without Ig therapy dependency (Table E1 in the Online Repository available at www.jacionline.org). Eight patients died after 24 months at year 2-3 (n = 4), year 4 (n = 2), or later (n = 2). Causes of death were infections (n = 5), secondary malignancy (n = 2), and other cause (n = 1; see Table E2 in the Online Repository). Patients were scored as alive and well without Ig supplementation in 15.8% of ADA-, 42.1% of DCLRE1C-, 47.1% of RAG-, and 57.5% of IL2Rγ-JAK3-IL7R–deficient patients ($P = .011$). Posttransplantation clinical problems were reported in 28 (18.4%) of 152 patients, with the lowest frequency in the IL2Rγ-JAK3-IL7R group (12.5%) and the highest in the DCLRE1C group (36.8%, $P = .096$). Sequelae were reported in 23 (15.1%) of 152 patients, with significant differences between the genetic subgroups: 57.9% of ADA-, 15.8% of DCLRE1C-, 10.0% of IL2Rγ-JAK3–, and 2.9% of RAG-deficient patients ($P < .001$; Table E1). A detailed description of reported clinical problems and sequelae is provided in Table E3 in the Online Repository.

Long-term IR and correlation with clinical outcome

IR data were collected at +1 year, +2 years, and LFU (median, 6.4 years; range, 2.8-10.8 years) in the same 152 patients. The analysis focused on total CD4 and naive CD4 T lymphocyte numbers as a surrogate marker for the quality of immune function. Naive CD4 T lymphocyte counts at 1 and 2 years after

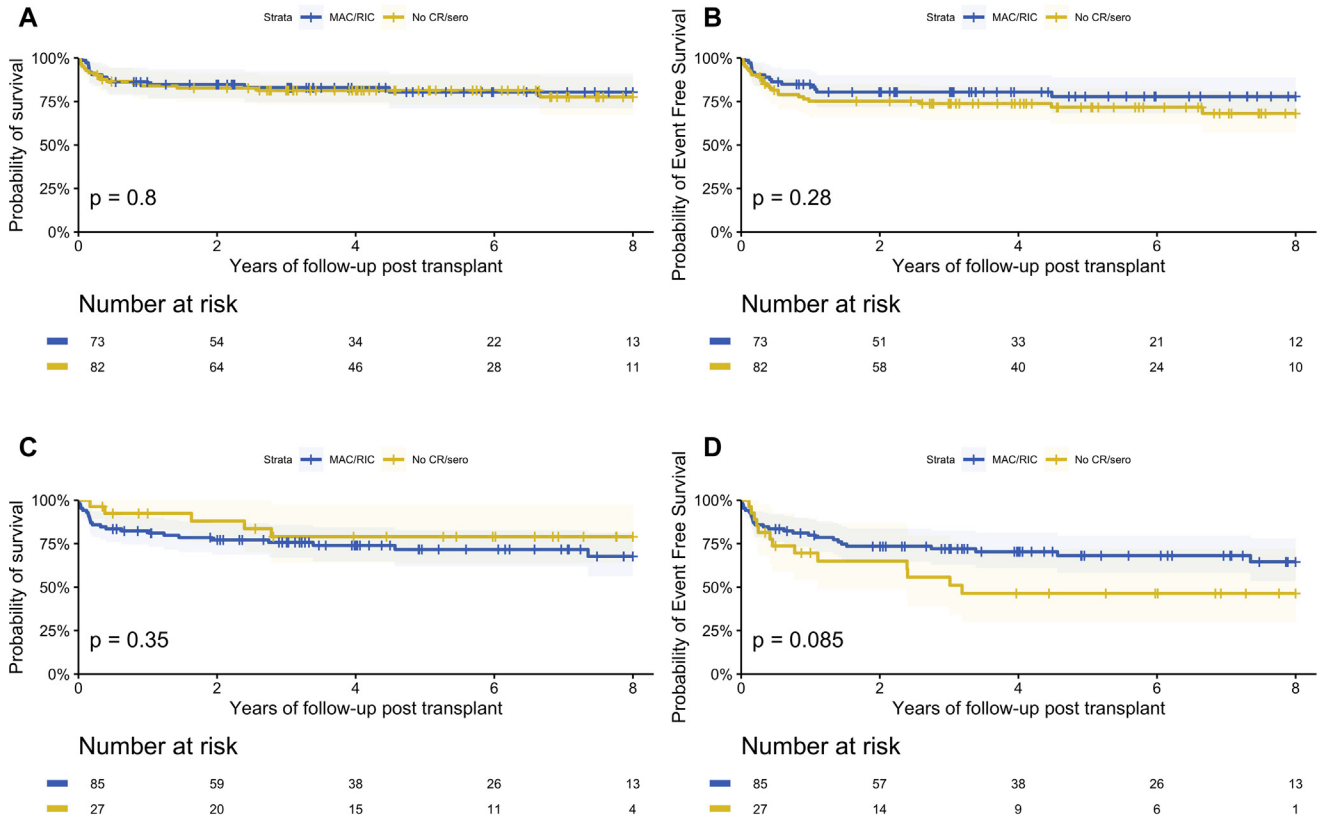

FIG 3. Impact of conditioning on OS and EFS in the IL2Rγ-JAK3-IL7R and RAG-DCLRE1C SCID subgroups. OS and EFS in patients with or without chemotherapy conditioning in IL2Rγ-JAK3-IL7R– (**A, B**; $P = .8$ and $P = .28$, respectively) and RAG-DCLRE1C–deficient (**C, D**; $P = .35$ and $P = .085$, respectively) SCID groups.

TABLE II. Multivariate adjusted survival analysis on OS and EFS

Characteristic	Variable	OS			EFS		
		HR	95% CI	*P* value	HR	95% CI	*P* value
SCID Group	ADA	1	—	—	1	—	—
	IL2Rγ-JAK3-IL7R	0.97	0.39-2.38	.94	0.88	0.42-1.84	.73
	RAG-DCLRE1C	1.36	0.56-3.35	.5	1.33	0.64-2.8	.45
	Other	2.18	0.77-6.15	.14	1.83	0.75-4.44	.18
Pre-HSCT relevant infections	Absent	1	—	—	1	—	—
	Present	2.32	1.44-3.72	<.001	1.99	1.33-2.98	<.001
Donor	Matched	1	—	—	1	—	—
	MMRD	2.46	1.3-4.67	.006	2.23	1.31-3.81	.003
	MMUD	1.96	0.8-4.8	.14	1.26	0.57-2.77	.57
Source of hematopoietic stem cells	BM	1	—	—	1	—	—
	Cord blood	1.08	0.44-2.64	.87	1.12	0.52-2.41	.78
	PBSC	1.28	0.7-2.34	.42	1.15	0.68-1.94	.59
Transplantation period	2006-2010	1	—	—	1	—	—
	2011-2014	0.74	0.44-1.23	.24	0.74	0.48-1.14	.17

PBSC, Peripheral blood stem cell.

transplantation showed a good correlation (adjusted R^2 0.53; see Fig E2, *A,* in this article's Online Repository at www.jacionline.org), whereas this correlation was less clear for total CD4 T lymphocyte numbers (data not shown). Naive CD4 T lymphocyte numbers showed the largest dispersion at the 1-year time point and gradually narrowed thereafter. Naive CD4 T lymphocyte profiles revealed that patients in the lower 2 quartiles at 1 year ($<0.5 \times 10^{e3}/\mu L$) remained in this lower range during the entire follow-up period (Fig E2, *B*). This pattern was observed in all genetic subgroups in the nonconditioned and MAC cohorts (Fig E2, *C*). The median naive CD4 T lymphocyte value was highest in the IL2Rγ-JAK3-IL7R subgroup at all evaluable time points, at $0.81 \times 10^{e3}/\mu L$; ADA was $0.22 \times 10^{e3}/\mu L$, and RAG-DCLRE1C was $0.47 \times 10^{e3}/\mu L$ (year 1; $P = .006$). In IL2Rγ-JAK3-IL7R patients, median naive CD4 T lymphocyte values were similar in the MAC and nonconditioned group during

TABLE III. Correlation between conditioning and Ig dependency at LFU

Characteristic	MAC (n = 71)	Reduced-intensity conditioning (n = 8)	None/serotherapy only (n = 65)	Total (N = 144)	*P* value
Ig independent at LFU					<.001
Yes	62 (87%)	6 (75%)	38 (59%)	106 (74%)	
No	9 (13%)	2 (25%)	27 (42%)	38 (26%)	

P values calculated by chi-square test, with continuity correction applied for 2 × 2 tables.

follow-up ($P = .93$) in the MD and MMD groups. In contrast, NK cell reconstitution in IL2Rγ-JAK3-IL7R patients was significantly better when treated with MAC compared to no conditioning (Fig E2, *D;* $P = .04$) compatible with engraftment of the respective progenitors and hematopoietic stem cells. In the RAG-DCLRE1C and ADA patients, naive CD4 T lymphocyte numbers were significantly lower in the nonconditioned compared to MAC patients (Fig E2, *C;* $P = .009$). In patients who had received MAC, median naive CD4 T lymphocyte recovery at 1 year was similar in the IL2Rγ-JAK3-IL7R (n = 24) and the RAG-DCLRE1C (n = 37) subgroups ($P = .106$). Umbilical cord blood graft recipients had significantly higher median naive CD4 T lymphocyte numbers compared to those grafted with BM after MAC at all evaluable time points (Fig E2, *E;* year 1, $P < .001$).

Ig replacement therapy dependence at LFU was reported in 26.4% of patients and was significantly lower in conditioned (11/79, 13.9%) compared to nonconditioned/serotherapy-only patients (27/68, 39.7%) (Table III, $P < .001$). Within the MAC group, Ig dependence was observed in 1 of 29 of IL2Rγ-JAK3-IL7R–deficient and 8 of 40 of RAG-DCLRE1C–deficient patients ($P = .10$) (Fig E2, *F*). Notably, Ig dependence strongly correlated with the number of naive CD4 T lymphocytes. At +1 year and +2 years, and particularly at LFU, a minor and decreasing fraction of patients with more than $0.5 \times 10^{e3}/\mu L$ naive CD4 T lymphocytes was dependent on Ig supplementation (Fig 4). To study the predictive level of naive CD4 T lymphocyte reconstitution on clinical outcome, logistic regression was applied (Fig E2, *G*). A threshold of 0.5×10^{e3} naive CD4 T lymphocytes/μL at 1 year after transplantation was identified to strongly correlate with favorable clinical outcome, defined as alive and well plus Ig independence as well as with alive with sequelae only (Table IV, $P = .017$ and $P < .001$, respectively). A weaker correlation was observed for CD4 T lymphocytes at 1 year after transplantation (cutoff level $0.75 \times 10^{e3}/\mu L$, $P = .019$ and $P = .003$, respectively). The low number of late deaths (>2 years after transplantation) did not allow for a correlative analysis with naive CD4 T lymphocytes at 1 year. Acute GvHD did not negatively affect naive CD4 T lymphocyte numbers at 1 year or Ig dependence (data not shown). In multivariate analysis, naive CD4 T lymphocyte counts, IL2Rγ-JAK3-IL7R–deficient SCID, and MAC were each positively correlated with a favorable outcome (ie, alive and well plus Ig independent), whereas a MMRD showed a negative correlation (Table V).

DISCUSSION

We report here what is to our knowledge the largest cohort of transplanted, genetically defined SCID patients as registered in SCETIDE, with a similar favorable outcome observed for all genotypes. Pretransplantation infections and MMRDs were identified as the main independent risk factors at transplantation for inferior OS and EFS. Moreover, we demonstrate that the level of naive CD4 T lymphocyte reconstitution at 1 year after HSCT strongly predicts long-term clinical and immunologic outcome.

Whereas previous studies consistently reported superior OS in the T^-/B^+ compared to T^-/B^- subgroup of SCID patients,[4,5] our study is the first to show similar OS and EFS can be achieved in these subgroups of SCID patients, specifically in IL2Rγ-JAK3-IL7R and RAG-DCLRE1C SCID subgroups. In contrast to a recent North American study,[7] but concordant with earlier observations by Schuetz et al,[12] we observed similar survival in the RAG- and DCLRE1C-deficient patients. This may be related to the fact that the patients in our study were transplanted in a more recent time period, and mainly with tailored conditioned transplants, which results in superior graft function. The favorable OS in ADA-SCID patients compared to other reports[7] may well be explained by the high proportion of patients transplanted using a MD—a bias likely related to inclusion of patients lacking a MD in gene therapy trials during the last decade and the use of enzyme replacement therapy.

Multivariate analysis identified relevant pretransplantation infections use of MMRDs as major independent risk factors associated with inferior OS and EFS. Our study confirms previous observations that pretransplantation infections are a strong independent predictor for unfavorable outcome after HSCT.[5,6,13] This emphasizes the crucial importance of early recognition of SCID patients to allow for timely initiation of protective measurements to bridge patients toward curative stem cell therapy treatment without infectious burden. Newborn screening programs have been established in many countries to achieve this goal, but no patients in this cohort were identified via newborn screening.[14]

In previous SCID studies, OS was consistently inferior in patients transplanted with unrelated donor compared to MSD.[5-7] Our study is the first to demonstrate similar OS in SCID patients transplanted with MSD and MUD, most likely reflecting the impact of high-resolution HLA typing on unrelated donor selection, and thereby a more precise manner to analyze the impact of matching grade on transplantation outcome. Our finding is in line with recent pediatric HSCT studies in non-SCID inborn errors of immunity.[15-17] Whereas our current and previous studies reported slightly less favorable outcome with MM(R)D, several recent studies in patients with inborn errors of immunity have reported encouraging results with MMUD and MMRD (haploidentical) donors using either TCR αβ/CD19 depletion or posttransplantation cyclophosphamide approaches.[18-22] Future studies will reveal whether these novel approaches may contribute to reduce the current gap in outcome between MD and MMD transplants and whether this will be the same for the different SCID genotypes. Eventually, the steadily improving transplantation results with alternative donors may have an implication for future donor hierarchy, and for the positioning of gene therapy, which is currently mainly reserved for patients lacking a MD and for which excellent results have recently been reported in ADA-SCID.[23]

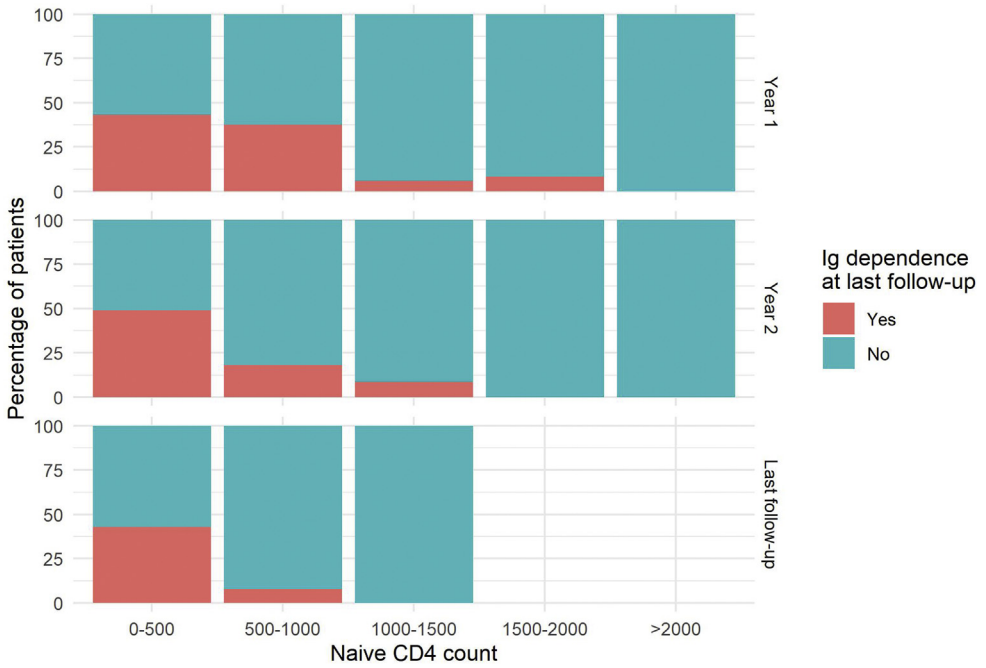

FIG 4. Ig dependence is correlated with naive CD4 T lymphocyte numbers. Dependency on Ig supplementation at LFU in relation to the numbers of naive CD4 T lymphocytes at different time points (+1 year, +2 years, LFU) after HSCT.

TABLE IV. Correlation between numbers of naive and total CD4 T lymphocytes at +1 year and clinical outcome

	Naive CD4 count at 1 year			CD4 count at 1 year		
Characteristic	**≤500 (n = 63)**	**>500 (n = 68)**	***P* value**	**≤750 (n = 58)**	**>750 (n = 88)**	***P* value**
Alive and well and Ig independent			.017			.019
Yes	22(35%)	39 (57%)		20(34%)	49 (56%)	
No	41(65%)	29 (3%)		38(66%)	39 (44%)	
Alive and well or only sequelae, Ig independent			<.001			.003
Yes	26 (41%)	49 (72%)		25 (43%)	61 (69%)	
No	37 (59%)	19 (28%)		33 (57%)	27 (31%)	

P values calculated by chi-square test, with continuity correction applied for 2 × 2 tables.

TABLE V. Multivariate analysis of being alive and well and Ig independent at LFU

					95% confidence interval		
Characteristic	**Variable**			**Odds ratio**	**Lower**	**Upper**	***P* value**
Naive CD4 T lymphocytes at 1 year (per 500 cells/μL)	1.62			1.18	2.30	.004	
Diagnosis	IL2Rγ-JAK3-IL7R			1.00			
	RAG-DCLRE1C			0.28	0.09	.78	.019
	ADA			0.09	0.02	.38	.002
Conditioning	MAC			1.00			
	None/serotherapy only			0.19	0.06	.57	.004
	Reduced-intensity conditioning			0.23	0.03	1.47	.12
Donor type	MSD	1.00					
	MRD	0.42	0.08	2.04	.3		
	MUD	0.99	0.21	4.66	>.9		
	MMUD	0.22	0.03	1.24	.092		
	MMRD	0.21	0.05	.78	.023		

In the last decades, there has been ongoing debate on the risk/benefit ratio of conditioning in SCID. Unconditioned infusions, predominantly used in T^-/B^+ SCID and in patients with severe, mostly infection-driven comorbidity, have often been lifesaving, mediated by protective donor T lymphocyte engraftment—with the caveat that GvHD remains a point of attention and IR longevity is not ensured.[24-26] Moreover, omitting intensive chemotherapy-based conditioning may reduce the occurrence of

general late effects like fertility, late cancers, or effects on neurocognitive development, as well as specific late effects in susceptible genetic subgroups like DCLRE1C SCID.[12] Still, in the absence of MAC, BM and thymic niches occupied by host progenitor cells will not be effectively depleted, thus preventing optimal repopulation by donor equivalents.[27] In those cases, thymic function and sustained output of naive donor–derived T lymphocytes is often insufficiently corrected. In addition to conditioning, the stem cell source may also have an impact on reconstitution because naive CD4 T lymphocyte reconstitution was more favorable with umbilical cord blood compared to BM in the setting of MAC. This has been reported previously and reflects the properties of fetal cord blood $CD4^+$ T lymphocytes.[28] Our results also highlight clear genotype-dependent differences, with the most pronounced reconstitution of naive CD4 T lymphocytes in IL2Rγ-JAK3-IL7R patients, which seems similar with or without conditioning at the time points analyzed in this study. The favorable IR likely contributes to the favorable clinical and immunologic outcome of this genetic subgroup, as observed in the multivariate analysis. In contrast, naive CD4 T lymphocyte numbers in RAG-DCLRE1C patients were significantly inferior in the absence of conditioning. Likewise, in the absence of MAC, B lymphocyte development will often not be successfully restored in B^- SCID variants or will remain of host origin in IL2Rγ/JAK3-deficient SCID, thereby maintaining the status of intrinsically impaired B lymphocyte function.[29] We here show that contemporary MAC, in contrast to previous experience,[7] is not associated with an inferior OS or increased occurrence of acute GvHD. This may reflect the recent use of less toxic regimens, the use of treosulfan or targeted (reduced intensity) busulfan plus fludarabine instead of 2 alkylating agents, as per the guidelines of the Inborn Errors Working Party.[30] Developments in antibody-based conditioning, targeting the stem cell niche without collateral systemic acute and late toxicity, may lead to future regimens with a more favorable profile.[31]

Detailed analysis of clinical and immunologic outcome in a representative subgroup of 152 patients showed that almost two thirds of these patients are alive and well at 2 or more years after HSCT, whereas half of the patients are alive and well without the need for Ig support, with no significant difference among the genetic subgroups, at least with this duration of follow-up. Sequelae were reported in 12.5% of patients; we observed an expected predominance in ADA- and DCLRE1C-deficient SCID, confirming previous reports.[7,12]

Restoration of sustained protective T lymphocyte, and preferably also B lymphocyte, immunity is the main goal of stem cell therapy in SCID patients. We demonstrate that reconstitution of naive CD4 T lymphocytes at 1 year is predictive for the further clinical course. These findings substantiate earlier reports on the predictive value of T-cell receptor excision circles early after transplantation for long-term T lymphocyte immunity.[24,25] We show for the first time in a multicenter study that the level of naive CD4 T lymphocytes ($> 0.5 \times 10^{e3}/\mu L$) at 1 year after transplantation strongly correlates with a favorable clinical outcome and Ig independence in the years thereafter. A recent study reporting outcome data on a cohort of patients transplanted over a much longer time period pointed to the predictive value of total CD4 ($>0.5 \times 10^{e3}/\mu L$) and naive CD4 T lymphocytes ($>0.2 \times 10^{e3}/\mu L$) at +6 and +12 months on OS, but it did not investigate the correlation with clinical outcome characteristics, as we did in our study.[7] As a result of the small number of late deaths in our cohort, we could not demonstrate a correlation between (naive) T lymphocyte reconstitution and survival. Our findings demonstrate that 0.5×10^{e3} naive CD4 T lymphocytes/μL at 1 year after transplantation strongly predicts a favorable clinical course and Ig dependency during further follow-up, and can therefore be instrumental to guide clinical decision making. Delmonte et al[32] recently reported preliminary data that TCR β repertoire early after HSCT represented a useful biomarker to predict T diversity of T lymphocyte reconstitution and also correlated with absolute numbers of naive CD4 T lymphocytes at 6 months.

In summary, we demonstrate that transplantation outcome in SCID patients has continued to improve in the recent time period. Serious pretransplantation infections and use of MMRDs remain associated with a less favorable outcome. Ongoing implementation of newborn screening programs, recent advances in MMD transplantation strategies, increasing availability of gene therapy options, and optimization of conditioning regimens will be the main tools to further improve survival, and particularly clinical and immunologic long-term outcome in SCID patients.

We would like to thank the medical and nursing staff and the data managers of the participating centers for their valuable contributions.

Key messages

- **In transplanted SCID patients, 2-year EFS is similar for genetic subgroups, while pretransplantation infections and use of MMRDs are associated with an unfavorable EFS.**
- **Naive CD4 T lymphocytes at the $>0.5 \times 10^{e3}/\mu L$ level at 1 year after transplantation strongly predict a favorable clinical course and lessened Ig dependency during further follow-up.**

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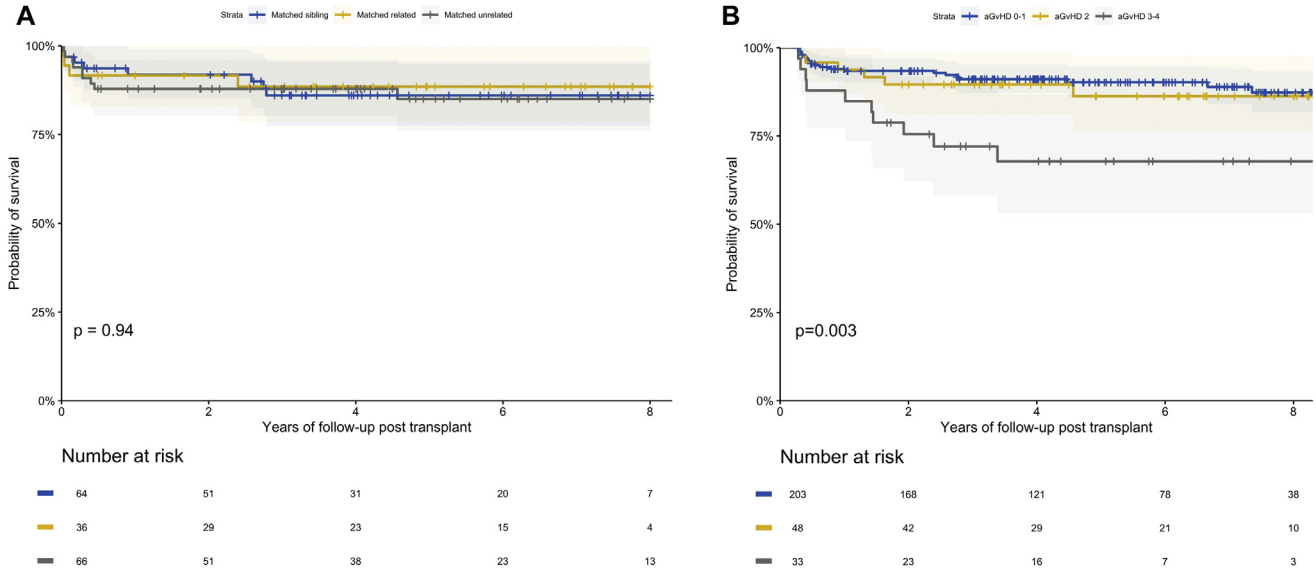

FIG E1. A, OS in MDs comparing MSDs, MRDs, and MUDs. OS is shown for SCID patients transplanted with 1 of the 3 MD types; MSDs, MRDs, and MUDs ($P = .94$). **B,** Impact of acute GvHD on OS. Impact of acute GvHD grade 0-1, grade 2, and grade 3-4 on OS using 3-month Landmark analysis ($P = .003$).

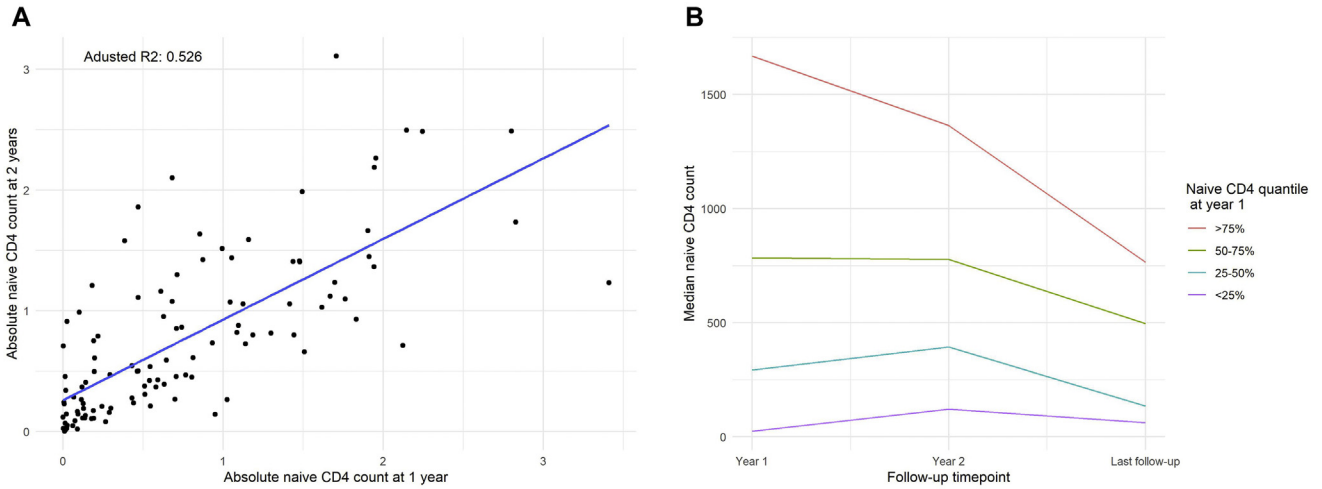

FIG E2. A, Correlation naive CD4 T lymphocytes at 1 and 2 years after HSCT. Correlation between absolute numbers of naive CD4 T lymphocytes measured at +1 and 2 years after HSCT (adjusted R^2, 0.526). **B,** Naive CD4 T lymphocyte levels at 1 and 2 years, and LF in per quantile (patient quantiles assigned by naive CD4 level in year 1). Absolute naive CD4 T lymphocyte levels at 1 and 2 years, and LF per quantile (patient quantiles assigned by naive CD4 level T lymphocyte numbers in year 1). **C,** Naive CD4 T lymphocyte numbers at +1 and +2 years and LFU (*top to bottom*) and matched versus mismatched transplantation (*left to right*) in the genetic subgroups in relation to type of conditioning. Naive CD4 T lymphocyte numbers at +1 and +2 years and LFU (*top to bottom*) in matched (*left column*) versus mismatched (*right column*) donor transplantation per genetic subgroup (ADA, IL2Rγ-JAK3-IL7R, and RAG-DCLRE1C) and in relation to type of conditioning: *red* indicates MAC; *blue,* reduced-intensity conditioning (RIC); *green,* no conditioning; and *purple,* serotherapy only. **D,** NK cell numbers at +1 and +2 years and LFU (*top to bottom*) and matched versus mismatched transplantation (*left to right*) in the genetic subgroups in relation to type of conditioning. Absolute numbers of NK cells at +1 and +2 years and LFU (*top to bottom*), in matched (*left column*) versus mismatched (*right column*) donor transplantation per genetic subgroup (ADA, IL2Rγ-JAK3-IL7R, and RAG-DCLRE1C) and in relation to type of conditioning: *red* indicates MAC; *blue,* RIC; *green,* no conditioning; and *purple,* serotherapy only. **E,** Naive CD4 T lymphocyte numbers at +1 and +2 years and LFU (*top to bottom*) and matched versus mismatched transplantation (*left to right*) in the genetic subgroups in relation to type of graft source. Absolute numbers of naive CD4 T lymphocyte numbers at +1 and +2 years and LFU (*top to bottom*), in matched (*left column*) versus mismatched (*right column*) donor transplantation per genetic subgroup (ADA, IL2Rγ-JAK3-IL7R, and RAG-DCLRE1C), and in relation to type of graft source: *red* indicates BM; *green,* cord blood; and *blue,* peripheral blood stem cells (PBSCs). **F,** Ig dependence at 1 and 2 year and LFU in relation to genetic subgroup and conditioning. Ig dependence (in percentage of patients, *y-axis*) at 1 and 2 years and LFU (*top to bottom*) in relation to genetic subgroup (ADA, IL2Rγ-JAK3-IL7R, and RAG-DCLRE1C, *left to right*) and conditioning (no MAC vs MAC). (**G**) CD4 naive and total CD4 numbers in relation to outcome (A/W and Ig independent). Absolute naive CD4 (*top*) and total CD4 T lymphocyte numbers (*bottom*) in relation to outcome (A/W and Ig independent; $P < .001$ and $P < .001$, respectively) using logistic regression analysis.

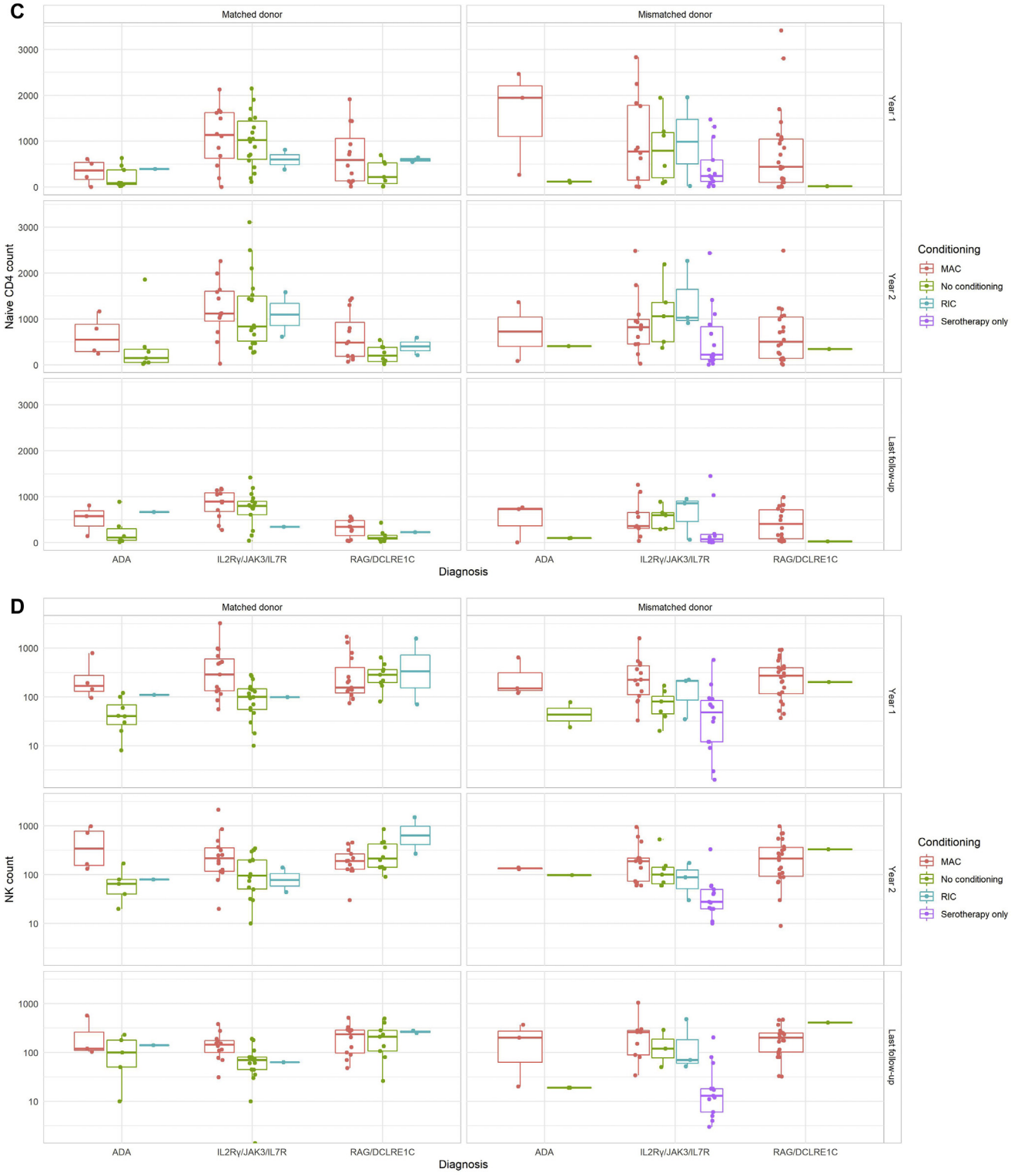

FIG E2. *(Continued).*

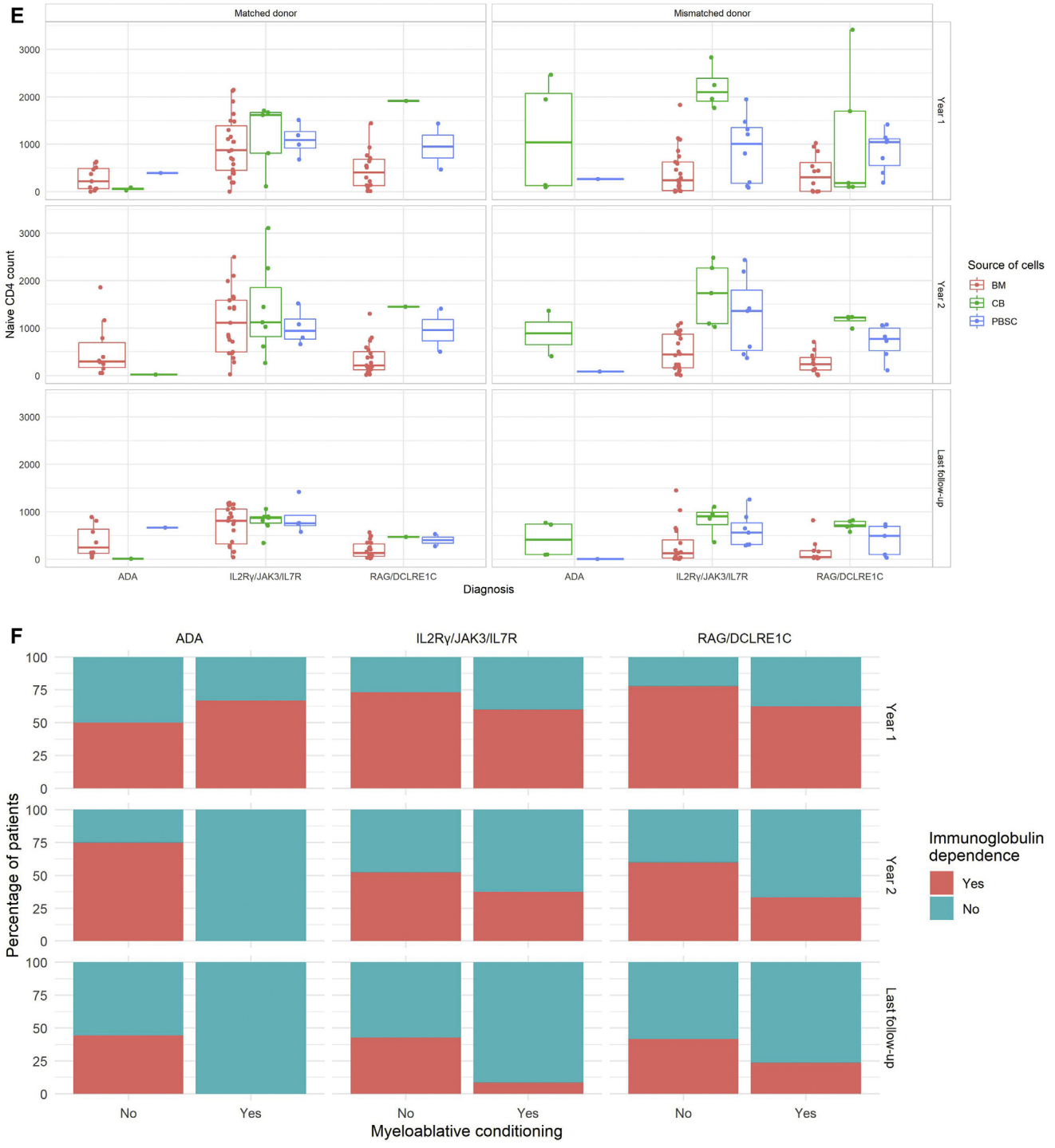

FIG E2. *(Continued).*

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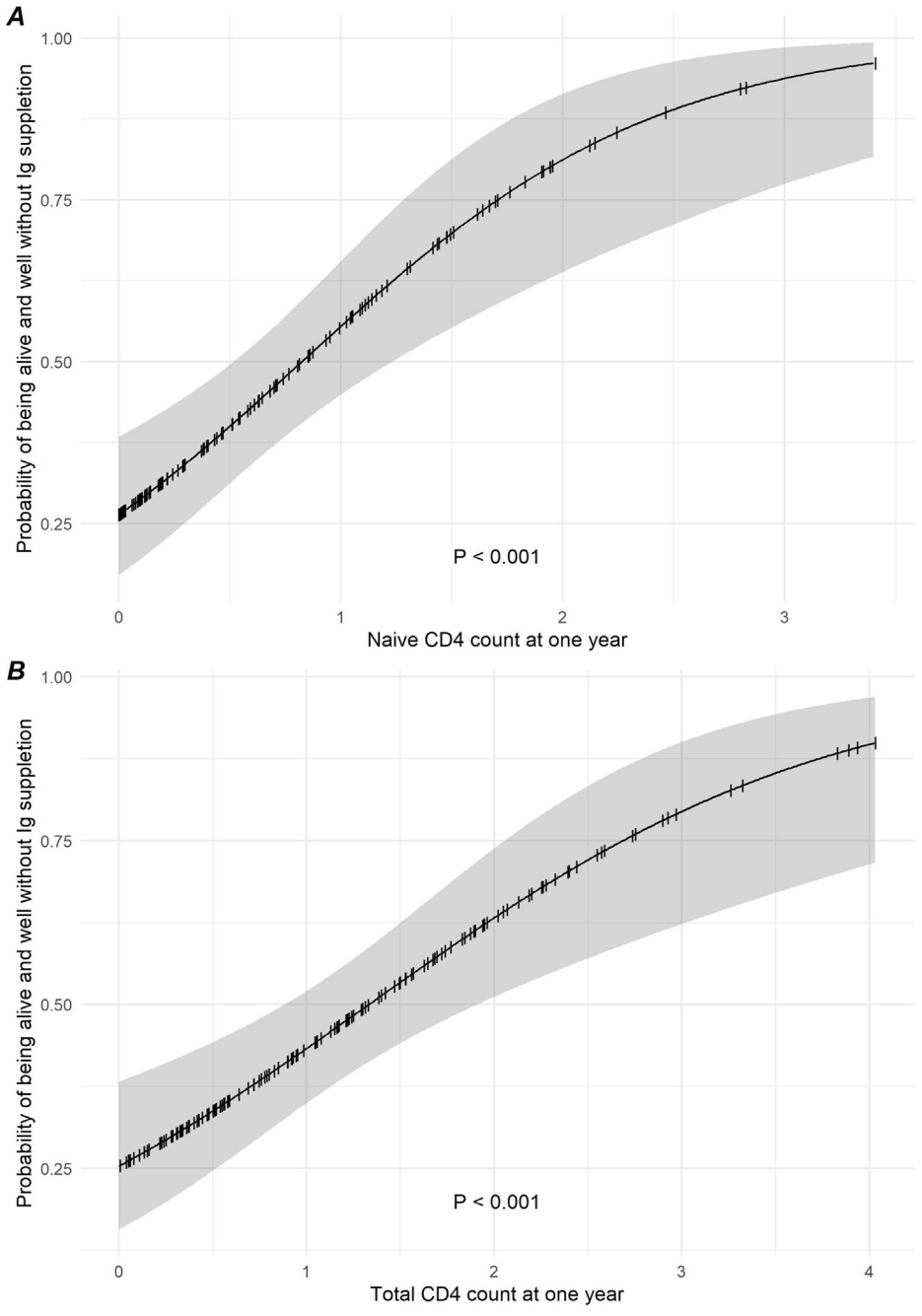

FIG E2. *(Continued).*

TABLE E1. Clinical outcome in 152 genetically defined SCID patients

	Total		ADA		DCLRE1C		RAG1/2		IL2Rγ		JAK3		IL7R	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Alive and well, without Ig therapy*	73	48	3	16	8	42	16	47	35	57	6	46	5	83
Alive and well, with Ig	20	13	1	5.5	1	5	6	17	9	15	3	23		
Alive with clinical problems, without Ig†	16	11	4	21	6	32	4	12	2	3				
Alive with clinical problems, with Ig†	12	8			1	5	3	9	6	10	2	15		
Alive with sequelae, without Ig	17	11	8	42	2	11	1	3	5	8	1	8		
Alive with sequelae, with Ig	6	4	3	15.5	1	5			2	3.5				
Late death	8	5					4	12	2	3.5	1	8	1	17
Total	152		19		19		34		61		13		6	4

*Three IL2Rγ and 1 JAK3 patients presenting warts.
†Including patients with sequelae.

TABLE E2. Causes of death

	Total		<1 year after HSCT		<1 and >2 years after HSCT		>2 years after HSCT	
Main cause of death	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Infection	71	67	59	68	5	62.5	7*	63.5
Toxicity	15	14	15	17				
GvHD	5	5	3	3.5	1	12.5	1	9
Nonengraftment	3	2.5	3	3.5				
Neoplasia	2	2					2†	18.5
Posttransplantation lymphoproliferative disease	1	1			1	12.5		
Other	3	2.5	2	2			1‡	9
Unknown	6	6	5	5	1	12.5		
Total	106		87	82	8	8	11	10

*Five patients from IR cohort.
†Two patients from IR cohort.
‡One patient from IR cohort.

TABLE E3. Clinical problems and sequelae in 152 genetically defined SCID patients

Characteristic	Total	ADA	DCLRE1C	RAG1/2	IL2Rγ	JAK3	IL7R
Clinical problems	47						
Endocrine dysfunction	7	2	3	1	1		
Nutritional deficiency with support	10	1	3	1	3	1	1
Liver disease	1				1		
Lung disease	7		1	2	3	1	
Renal disease	1			1			
Other autoimmunity*	14	2	1	4	6	1	
Autoimmune cytopenia	3			3			
Neoplasia	3			2†		1‡	
Other	1				1		
Sequelae	40						
Growth retardation	12	2	5	1	3		1
Hearing loss	12	10		2			
Neurocognitive and motor impairment	9	4	1	1	2	1	
Sequelae from infection	2				2		
Orthopedic problems	3	1	1	1			
Other	2	1		1			
Serious infection	8			2	2	3	1
Persistent chronic GvHD	5			3	2		
Second transplant (>2 years after first)	3			2		1	
Late death	8			4	2	1	1

Patients could have more than 1 clinical problem.
*Hepatitis (n = 5), dysthyroidism (n = 4), skin (n = 3), myasthenia (n = 1), oligoarticular juvenile idiopathic arthritis (n = 1).
†Osteosarcoma (n = 1), acute lymphoblastic leukemia (n = 1).
‡Osteosarcoma (n = 1).