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2021 L Street NW, Suite 900,
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Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

Allogeneic stem cell transplantation compared to conservative management in adults with inborn errors of immunity.

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Morgane Cheminant (Université de Paris, Institut Imagine, Laboratory of hematological disorders, INSERM UMR1163, F-75015, Paris, France, France) Thomas Fox (Department of Immunology, Royal Free London NHS Foundation Trust, United Kingdom) Mickael Alligon (French National Reference Centre for Primary Immunodeficiencies (CEREDIH), France) Olivier Bouaziz (MAP5 (UMR CNRS 8145), Université Paris Cité, France) Bénédicte Neven (French National Reference Centre for Primary Immunodeficiencies, France) Despina Moshous (French National Reference Centre for Primary Immunodeficiencies, France) Stephane Blanche (French National Reference Centre for Primary Immunodeficiencies, France) Aurélien Guffroy (CNRS / Université de Strasbourg / Hôpitaux Universitaires de Strasbourg,) Claire Fieschi (French National Reference Centre for Primary Immunodeficiencies, France) Marion Malphettes (Hôpital Saint Louis, France) nicolas schleinitz (CHU Timone, AP-HM, AMU, France) antoinette perlat (CHU Rennes, France) Jean-François Viallard (Haut-Leveque Hospital, France) Nathalie Dhedin (SAINT LOUIS HOSPITAL, France) Francoise Sarrot-Reynauld (Service de Médecine Interne, CHU Grenoble-Alpes, France) Isabelle durieu (Université de Lyon-Hospices civils de lyon, France) Sebastien Humbert (Internal Medicine Department., France) Fanny FOUYSSAC (Children's Hospital, France) Vincent Barlogis (assistance publique des Hopitaux de Marseille, France) Benjamin Carpenter (Department of Haematology, University College Hospital NHS Trust, United Kingdom) Rachael Hough (UCLH, United Kingdom) Arian Laurence (Royal Free London NHS Foundation Trust, United Kingdom) Ambroise Marçais (Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Necker Enfants-Malades, France) Ronjon Chakraverty (University College London Hospital NHS Foundation Trust, United Kingdom) Olivier Hermine (Clinical Haematology, Necker-Enfants malades University Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), France) Alain Fischer (French National Reference Centre for Primary Immunodeficiencies, France) Siobhan Burns (Department of Immunology, Royal Free London NHS Foundation Trust, United Kingdom) Nizar Mahlaoui (French National Reference Centre for Primary Immunodeficiencies (CEREDIH), France) Emma Morris (Dept Haematology, University College London Hospitals NHS Foundation Trust, United Kingdom) Felipe Suarez (French National Reference Centre for Primary Immunodeficiencies (CEREDIH), France)

Abstract:
Allogeneic hematopoietic stem cell transplantation (alloSCT) is curative for severe inborn errors of immunity (IEI), with recent data suggesting alloSCT in adulthood is safe and effective in selected patients. However, questions remain regarding the indications for and optimal timing of transplant. We retrospectively compared outcomes of transplanted with matched non-transplanted adults with severe IEI.

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Non-author contributions and disclosures: Yes; Members of the CEREDIH French PID study group, not included as authors. We listed as main authors scientists and physicians who designed the study, analyze the data and wrote the manuscript, as well as the physicians who took care of more than 3 patients. The others have been listed as corporate authorship in the group named as "members of the CEREDIH French PID study group". 1. Aude Marie Cardine (Department of Paediatric Oncology, Rouen University Hospital, F76000, Rouen, France) 2. Thibault Comont (Department of internal medicine, Toulouse University Hospital, Institut universitaire du cancer de Toulouse, and University of Toulouse, F-31059, Toulouse, France) 3. Pierre Cougoul (Immunopathologie-medecine interne, IUC T Oncopole, Toulouse, F-31059, Toulouse, France) 4. Maud D'Aveni (Université de Lorraine, CHRU Nancy, Hematology Department, Nancy, France) 5. Eric Deconinck (Service d'Hématologie, Centre hopitalier universitaire Besancon, Besancon, France) 6. Luminata Luca (Service de Médecine Interne et Maladies Infectieuses, CHU Poitiers, Poitiers, France) 7. Lionel Galicier (Department of Internal Medicine, Hôpital Saint Joseph, Marseille, France) 8. Martine Gardembas (Department of Hematology, CHU, Angers, France) 9. Cécile Goujard (Service de médecine interne et immunologie clinique, C HU Bicêtre, AP-HP, Université Paris Sud, Le Kremlin-Bicêtre, France) 10. Clément Gourguechon (Department of Internal Medicine, Amiens University Hospital, France) 11. Julie Graveleau (Department of Internal Medicine, Saint-Nazaire Hospital, France) 12. Arnaud Jaccard (Service d'Hématologie Clinique, CHU Dupuytren, Limoges, France) 13. Jean-Philippe Jais (Department of Biostatistics, Hôpital Necker, University of Paris, Paris, France; Institut Imagine, Unité INSERM 1163, Paris, France) 14. Roland Jaussaud (Department of Internal Medicine and Clinical Immunology, Regional Competence Center for Systemic and Autoimmune Rare Diseases, Nancy University Hospital, Lorraine University, Vandoeuvre-lès-Nancy, France) 15. Pierre-Yves Jeandel (Service de Médecine Interne, Centre Hospitalier Universitaire de Nice, Nice, France) 16. Eric Jeziorski (Department of Pediatrics, Infectious Diseases and Immunology, CHU Montpellier, Montpellier, France) 17. Guillaume Le Guenno (CHU de Clermont-Ferrand, Clermont-Ferrand, France) 18. Guillaume Lefevre (Department of Internal Medicine, Lille University Hospital, Lille, France) 19. Fleur Lerebours (Toulouse University Hospital, Toulouse, France) 20. Dalila Nouar (Service d'Immunologie Clinique et d'Allergologie, Centre Hospitalier Régional Universitaire, Tours, France) 21. Pierre-Simon Rohrlich (Pediatric Hematology Unit, L'Archet Hospital, CHU Nice, Nice, France) 22. Amélie Servettaz (Service de Médecine Interne, Maladies Infectieuses et Immunologie Clinique, CHU Reims, Hôpital Robert Debré, Reims, France) 23. Martin Silva Nicolas (Department of Internal Medicine, CHU de Caen Normandie, 14000, Caen, France) 24. Laurent Siproudhis (Department of hepato-gastroenterology, CHU Rennes - Hôpital Pontchaillou, Rennes, France) 25. Louis Terriou (Service de Médecine Interne, Institute for Translational Research in Inflammation University of Lille, Inserm, CHU Lille, 59000 Lille, France)

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Authors:

Morgane Cheminant, M.D., Ph.D. (1, 2, 3) ; Thomas A. Fox, M.D., Ph.D. (4, 5, 6) ; Mickael Alligon, B.Sc. (3) ; Olivier Bouaziz, Ph.D. (7) ; Bénédicte Neven, M.D., Ph.D. (3, 8) ; Despina Moshous, M.D., Ph.D. (3, 8, 9) ; Stéphane Blanche, M.D. (3, 8) ; Aurélien Guffroy, M.D., Ph.D. (10) ; Claire Fieschi, M.D., Ph.D. (3, 11, 12) ; Marion Malphettes, M.D., Ph.D. (11) ; Nicolas Schleinitz, M.D., Ph.D. (13) ; Antoinette Perlat, M.D. (14) ; Jean-François Viallard, M.D., Ph.D. (15) ; Nathalie Dhedin, M.D., Ph.D. (16) ; Françoise Sarrot-Reynauld, M.D., Ph.D. (17) ; Isabelle Durieu, M.D., Ph.D. (18) ; Sébastien Humbert, M.D. (19) ; Fanny Fouyssac, M.D., Ph.D. (20) ; Vincent Barlogis, M.D., Ph.D. (21); Benjamin Carpenter, M.D., Ph.D. (6); Rachael Hough, M.D. (6); Arian Laurence, M.D., Ph.D. (5, 6); Ambroise Marçais, M.D., Ph.D. (1); Ronjon Chakraverty, M.D., Ph.D. (4, 5, 6); Olivier Hermine, M.D., Ph.D. (1, 2, 3); Alain Fischer, M.D., Ph.D. (3, 8, 22); Siobhan O. Burns, M.D., Ph.D. (4, 5) ; Nizar Mahlaoui, M.D., Ph.D. (3, 8) ; Emma C. Morris*, M.D., Ph.D. (4, 5, 6) ; Felipe Suarez*, M.D., Ph.D. (1, 2, 3); **members of the CEREDIH French PID study group#**

Affiliations: (1) Clinical Haematology, Necker-Enfants malades University Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France; (2) Université de Paris, Institut *Imagine*, Laboratory of hematological disorders, INSERM UMR1163, F-75015, Paris, France; (3) French National Reference Centre for Primary Immunodeficiencies (CEREDIH), France; (4) UCL Institute of Immunity &

Transplantation, UCL, London, UK; (5) Department of Immunology, Royal Free London NHS Foundation Trust, London, UK; (6) Dept Haematology, University College London Hospitals NHS Foundation Trust, London, UK; (7) MAP5 (UMR CNRS 8145), Université de Paris; (8) Service d'hématologie-immunologie et rhumatologie pédiatrique, Necker-Enfants malades University Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France; (9) Université de Paris, Institut *Imagine*, Laboratory Genome Dynamics in the Immune System, INSERM UMR1163, F-75015, Paris, France; (10) Department of clinical immunology and internal medicine, National Reference Center for Autoimmune Diseases, Hôpitaux Universitaires de Strasbourg, Strasbourg, France; (11) Service d'Immunopathologie clinique, CHU Saint Louis, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France; (12) UMR 976, Université de Paris, France ; (13) Département de Médecine Interne, Hôpital de la Timone AP-HM, Aix-Marseille Université; (14) Service de médecine interne, CHU Rennes - Hôpital Pontchaillou, Rennes, France; (15) Médecine interne, Hôpital Haut-Lévèque, Pessac, France; (16) Haematology Adolescents Young Adults, Saint-Louis Hospital, Assistance Publique-Hôpitaux de Paris (APHP), Paris, France ; (17) Pôle pluridisciplinaire de médecine, Clinique de médecine interne, Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France; (18) Internal Medicine and Vascular Pathology Department, Adult Cystic Fibrosis Center, Groupement Hospitalier Lyon-Sud, Hospices Civils de Lyon, Pierre-Bénite, France ; (19) Service de médecine interne, Centre hospitalier régional universitaire de Besançon, Besançon ; (20) Hématologie oncologie pédiatrique, C HU de Nancy - Hôpitaux de Brabois, Nancy ; (21) Onco-hématologie pédiatrique, AP-HM, Hôpital La Timone, Université Aix-Marseille, Marseille ; France ; (22) Collège de France, Paris, France.

#Members of the CEREDIH French PID study group are listed in the supplementary appendix

***The authors contributed equally to this work.**

Correspondence:
Professor Felipe Suarez, Department of Clinical Hematology, Necker-Enfants malades University Hospital, 149 rue de Sèvres, 75015 Paris, France.
Phone: +33-144-495-282
Fax: +33-144-385-290
E-mail: felipe.suarez@aphp.fr

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Keypoints:

1. Non-transplanted adults with CGD and CID have an ongoing risk of severe events compared to transplanted patients.
2. AlloSCT prevents progressive morbidity associated with IEI in adults, which may outweigh the negative impact of TRM.

ABSTRACT

Allogeneic hematopoietic stem cell transplantation (alloSCT) is curative for severe inborn errors of immunity (IEI), with recent data suggesting alloSCT in adulthood is safe and effective in selected patients. However, questions remain regarding the indications for and optimal timing of transplant. We retrospectively compared outcomes of transplanted with matched non-transplanted adults with severe IEI.

Seventy-nine patients (aged ≥15 years) underwent alloSCT between 2008 and 2018 for IEI, including chronic granulomatous disease (CGD, n=20) and various combined immune deficiencies (CID, n=59). A cohort of non-transplanted patients from the French CEREDIH registry was identified blindly for case-control analysis after matching for birth decade, age at last review greater than age at alloSCT, CGD or CID, and autoimmune/lymphoproliferative complications; with ≤3 matched controls per index patient without replacement.

281 patients were included (79 transplanted, 202 non-transplanted). Median age at transplant was 21 years. Transplant indications were mainly lymphoproliferative disease (n=23) or colitis (n=15). Median follow-up was 4.8 years (IQR [2.5-7.2]). One-year TRM was 13%. Estimated DFS at 5 years was higher in transplanted patients (58% *vs*. 33%, p=0.007). Non-transplanted patients had an ongoing risk of severe events with an increased mean cumulative number of recurrent events compared to transplanted patients. Sensitivity analyses removing patients with CVID and their matched transplanted patients confirm these results. AlloSCT prevents progressive morbidity associated with IEI in adults, which may outweigh the negative impact of TRM.

INTRODUCTION

Inborn errors of immunity (IEI) are a heterogeneous group of diseases leading to a predisposition to infections, autoimmune or autoinflammatory manifestations, lymphoproliferation and malignancies. In less severe IEI near-normal life expectancy can be achieved with supportive care. However, in many IEI, life-threatening complications severely compromise quality of life and result in premature mortality. Allogeneic stem cell transplantation (alloSCT) is the standard of care for patients with severe combined immune deficiency and is commonly performed for children with various life-threatening IEI[1–6]. In older patients, transplant outcomes were historically poor and despite improved results with reduced-intensity conditioning (RIC), indications for and timing of transplant remain controversial in older patients[7]. The role of non-alloSCT therapies such as targeted agents and the so far exceptional gene therapy techniques in treatment algorithms for older patients are still mostly undefined[8–11].

Risks of alloSCT in older patients are outweighed by the potential benefits in IEI with predictably severe clinical phenotype, such as primary HLH or inherited bone marrow failure. However, decisions around transplantation in IEI with a variable clinical phenotype or sparse long-term outcome data are more challenging[11–19]. This includes patients with immunodeficiency affecting cellular and humoral immunity termed combined immunodeficiencies (CID), including immune dysregulation syndrome (IDS), late onset CID (LoCID) and common variable immune deficiency with serious non-infectious complications ('complex-CVID'), as well as patients with chronic

granulomatous disease (CGD) remaining reasonably well until adulthood without prior alloSCT.

In adults with severe IEI, comorbidities and organ dysfunction are frequent leading to higher transplant-related mortality (TRM) rates[20–22]. In order to reduce the TRM, RIC regimens have been used. A large prospective study demonstrated that RIC-alloSCT was safe and effective in patients with CGD, including 25 (45%) adolescent and young adults (14-39 years)[23]. In addition, more recent data has demonstrated that RIC approaches in carefully selected patients result in excellent overall survival (OS) in young adult patients[11,24]. We have recently reported similarly excellent outcomes after reduced-intensity conditioned alloSCT in adult IEI patients (85.2% 3-year OS)[25]. Very recently, a large retrospective study of alloSCT in CGD reported excellent outcomes with a 76% 3-year OS for patients ≥18 years, independent of conditioning regimen used[22], in line with a recent EBMT retrospective study demonstrating no impact of conditioning intensity on OS in a wider group of IEI transplanted ≥15 years[26].

Prospective randomized clinical trials are not possible in rare diseases with heterogeneous clinical presentations. In order to determine the risks and benefits of alloSCT in older IEI patients, we performed a matched pair analysis of transplanted adult patients with non-transplanted control patients and compared their outcomes.

PATIENTS AND METHODS

Patients

The study population included all IEI patients recorded in the French National Reference Center for IEI (CEREDIH) or the Royal Free London Hospitals (RFH) registries. All living patients gave their written informed consent (**Supplementary data**). Transplanted patients were included if they fulfilled the following criteria: (a) age at first alloSCT ≥ 15 years; (b) transplanted between January 2008 and December 2018; (c) IEI diagnosis of CGD or CID. The CID group included patients diagnosed with an IDS, LoCID or CVID according to the diagnostic framework of the referring physician (**Supplementary Table 1**). Twenty-two patients have been previously reported[25]. Data were collected retrospectively from the medical notes and registries. The dataset was censored in November 2019.

AlloSCT procedure

Conditioning regimens were classified as full-intensity conditioning or reduced intensity conditioning regimens (including intravenous busulfan ≤ 9.6 mg/kg total dose) as previously described[27]. For CGD patients, the recommended conditioning regimen is based on a large study showing the safety of a RIC regimen consisting of high-dose fludarabine, serotherapy and low-dose or targeted busulfan administration[23]. For CID patients, the clinical practice is more heterogenous and depends on the patient's comorbidities, the characteristics of the underlined IEI and the usual practice in the center. The recently published updated EBMT/ESID inborn errors working party guidelines for alloSCT for IEI include a chapter on recommendations for the management of adolescent and adult patients together with

guidance on disease-specific conditioning regimens[28]. Patients and donors were matched for HLA-A, -B, -C, -DRB1, and -DQB1 by intermediate or high-resolution DNA typing as appropriate. Peripheral blood chimerism was defined as "mixed" if donor DNA was ≤ 95%. The pretransplant hematopoietic cell transplantation-specific comorbidity index (HCT-CI) scores pretransplant were calculated for all patients[29,30].

Matching procedure

In order to accurately match alloSCT patients with non-transplanted control patients, we defined matching criteria based on both patient and IEI (underlying disease and comorbidities) characteristics. Matched non-transplanted patients were collected from the French CEREDIH registry database. Matching criteria were (a) decade of birth; (b) age at last review greater than age at alloSCT; (c) one of two IEI categories (CGD *vs*. CID, where CID included profound T-cell deficiency, CVID and IDS); (d) severity of CID patients (including autoimmune/inflammatory manifestation and/or malignant lymphoproliferative disease) (**Supplementary data and supplementary Table 2**). A random draw without replacement was then performed to select up to three controls per index case. Sensitivity analyses were performed to validate the matching and to identify the impact of the different numbers of CVID patients and/or lung involvement within the CID transplant and non-transplant groups on outcomes. To do that, we repeated the comparisons of both cohorts by removing patients identified as CVID and/or with lung involvement and their matched transplanted patients, without breaking the matching.

Statistics

Categorical and continuous variables were compared by either χ^2 or Fisher exact tests where relevant and by Mann-Whitney test, respectively. The baseline of all survival analyses was the age at alloSCT (randomization age for the controls). OS was defined as the time between baseline until death from any cause, and disease-free survival (DFS) as time between baseline and IEI-related events (defined by infection requiring hospitalization, severe autoimmune or inflammatory manifestation requiring systemic immunosuppression, malignancy) or death, whichever occurred first. Patients with no event were censored at the time of their last follow-up. The probability of dying from transplant-related complications (TRM) was estimated. To further analyze outcomes for patients who survived the first year following transplant, conditional overall survival (COS) was defined as the probability of surviving an additional number of years given that the patient has already survived one year. OS, COS and DFS curves were estimated using the Kaplan-Meier estimator and comparisons between alloSCT and non-transplanted patients were performed using the log-rank test. We then estimated the mean cumulative number of recurrent events (REs) using the Ghosh's estimator[31], which accommodates for the competing risk of death. REs were categorized as IEI and/or alloSCT-related events (defined as infection requiring hospitalization, severe autoimmune or inflammatory manifestations, malignancy, grade 3-4 acute and extensive chronic GVHD, graft failure, $CD34^+$ cell top up, donor lymphocyte infusion (DLI), post-transplant lymphoproliferative disease, viral reactivation requiring systemic anti-viral or cellular therapies). We emphasize that accounting for competing risks is critically important for this study as deceased patients can no longer be considered at risk for experiencing REs. Without incorporating competing risks into the analysis, an overestimation of the mean cumulative number of REs would occur. Cox regression models were implemented

for death (from all causes) and for REs. The Cox model for death was clustered on match criteria and included the identified risk factors (sex, birth decade, IEI category (CGD or CID), genetic diagnosis, lymphoproliferative disease, autoimmunity, aspergillosis, solid cancer, age more or less than 25 years old at alloSCT) as well as treatment group (alloSCT *vs*. non-alloSCT) with backward selection (selection criteria was $\alpha = 0.2$, lymphoproliferative disease, autoimmunity, aspergillosis, alloSCT *vs*. non-alloSCT). Moreover, considering that complications have a limited impact on survival after five years, complications were coded in the Cox model as binary time-dependent covariates which indicate at any time point if patients had the complication in the last five years or not. The Cox model for REs was implemented with the same set of covariates and robust sandwich standard error estimates were used to adjust for multiple events for the same patient[32]. In both Cox models, time dependent covariates were taken into account using the counting process approach[33] (https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf) (**Supplementary Figure 1**). All analyses were performed using R software version 3.6.1 (R Core Team 2018).

RESULTS

Patients' characteristics at baseline

In total, 281 patients were included, comprising 79 transplanted and 202 non-transplanted patients. Twenty CGD and 59 CID patients received a first alloSCT between 2008 and 2018 in London or in France (**Figure 1**). According to matching criteria, patients were equally distributed with respect to age at last review (median age 25y, IQR [20–30] *vs*. 26y, IQR [21–33] in non-transplanted patients, $p = 0.152$), IEI category (CGD or CID), and lymphoproliferative disease (28% *vs*. 24% in non-transplanted patients, $p = 0.533$). The distribution of IEI diagnoses was different in CID patients ($p < 0.001$), with less CVID diagnoses (1% *vs*. 31% in non-transplanted patients) and more profound T-cell deficiencies (73% *vs*. 45% in non-transplanted patients) (**Supplementary Table 3**). However, non-transplanted patients identified as CVID by their referring physician were similar to those identified as LoCID/IDS in terms of IEI-related complications (**Supplementary Table 4**). Moreover, a profound T-cell deficiency (identified by CD4<200/mm3 or naive T-cell deficiency) was identified in 19% of CVID patients. In contrast 30% of CID/IDS patients did not have a quantitative T-cell deficiency (**Supplementary Table 5**). Transplanted CID patients had higher comorbidity scores, with an increased incidence of prior or active infections compared to the non-transplanted CID control group ($p < 0.001$). Non-transplanted CID patients had more frequent interstitial pulmonary involvement (3% in transplanted *vs*. 15% in non-transplanted patients, $p = 0.017$). Of the 23 non-transplanted patients with lung involvement, 9 had CTLA-4/LRBA deficiency (**Table 1**). Patients with CGD had similar comorbidities between the two groups (**Table 2**).

Indications for allogeneic stem cell transplantation in the transplanted group and reasons for non-referral to alloSCT in the control non-transplanted group

Common reasons for transplant referral were lymphoproliferative disease (n=22/79) or gastrointestinal complications of IEI (n=15/79) (**Table 3)**. CGD patients were transplanted for colitis (n=8/20, 40%) or infection (n=12/20, 60%), mainly invasive aspergillosis (n=9/20, 45%). CID patients were mostly transplanted for malignant lymphoproliferative disease (n=22/59, 37%), including three patients with Wiskott-Aldrich syndrome, three with XLP1 (*SH2D1A*), two with activated PI3K-delta syndrome (APDS, *PIK3R1* and *PIK3CD* mutations) and eight with genetically undefined CID. In addition, seven CID patients were transplanted for colitis (including three with XLP2, *XIAP*), seven for infection, eight for autoimmune neutropenia (including three with hypomorphic RAG deficiency), seven for liver involvement (including three with CD40-ligand deficiency), two for hemophagocytic syndrome and two Wiskott-Aldrich patients for renal and cutaneous vasculitis. Only one patient was asymptomatic and preemptively transplanted following a diagnosis of XLP1 in the context of family screening (**Supplementary Table 6**).

Overall, only 12 (6%) of the non-transplanted control IEI patients received alloSCT after the end of the study. One-hundred and thirty-six (67%) of the non-transplanted control IEI patients did not receive alloSCT because of non-referral to a specialized centre to discuss the indication of alloSCT (n=81), an initial milder clinical phenotype or a late presentation (n=39), the absence of antigen appropriately matched donor (n=5) and patient choice (n=11). Moreover, targeted therapies are now available for some monogenic IEI, such as CTLA-4/LRBA deficiency or APDS, and alloSCT may be delayed in these patients. The role of alloSCT remains uncertain for a few IEI, such as CVID. They all received anti-infective treatments for curative or prophylactic

purposes (mainly antibiotics and antifungals). Ongoing immunoglobulin replacement therapy was given to 106 of 186 patients with available data. Autoimmune and inflammatory diseases were treated with corticosteroids (n=141), other immunosuppressive agents (n=55) and/or abatacept (n=7). Fifty-two patients received rituximab (either alone or in combination) for autoimmune or lymphoproliferative complications. The 48 patients with lymphoproliferation were treated with chemotherapy (n=35) including autologous stem cell transplantation (n=4), rituximab alone (n=2) or splenectomy (n=7) (NA for 5 patients). In total, 17 patients had splenectomy. Two patients received liver transplantation and one patient had lung transplant.

Allogeneic stem cell transplantation procedures

Fourteen females (18%) and 65 males (82%) received an alloSCT at a median age of 21 years (IQR [17–28], **supplementary Figure 2A**). The median time from age at clinical diagnosis of IEI to alloSCT was 13.3 years (IQR [5.0-19.2]). Most of the patients were transplanted after 2015 (n=47/79, **supplementary Figure 2B**). Forty-six patients received RIC (58%) and 33 myeloablative conditioning regimens (42%)[27]. Conditioning for CGD patients consisted of fludarabine, busulfan with alemtuzumab for 9 patients or rabbit ATG for 11 patients. Patients with CID mainly received fludarabine combined with melphalan 140 mg/m2, busulfan, or treosulfan. Patients transplanted with an haploidentical donor received a Baltimore regimen using high-dose posttransplant cyclophosphamide[34]. Details are shown in **Table 4**. Thirty patients had matched related donors (MRD; siblings), 33 matched unrelated donors (MUD; 10/10 antigen matched unrelated donor), twelve mismatched unrelated donors (MMUD; with 1 antigen mismatched unrelated donor) and four haploidentical donors.

Sixty-five patients were transplanted using serotherapy-containing regimens (alemtuzumab or anti-thymocyte globulin) for *in vivo* T-cell depletion. GVHD prophylaxis included cyclosporine combined with MMF in 73% of patients transplanted with MRD or MUD and 67% of patients transplanted with MMUD (see further details in **Supplementary Tables 6 and 7**). Ten patients (13%) had a morbidity HCT-CI of 0 whereas 24 (31%) had a score of >=3 (**Table 4)**.

With a median follow-up of 4.8 years (IQR [2.5-7.2]), 61 (77%) patients were alive following alloSCT. Of the surviving patients, 90% (55/61) were in remission with respect to the underlying IEI, notably 80% (49/61) in complete remission without transplant-related complications, including eight patients with mixed chimerism at last review (**Figure 2 and Supplementary Table 10**). AlloSCT survivors experienced a continuous improvement in outcome over time, including those with mixed chimerism. Eighteen patients died after alloSCT, including 14 of TRM and four of IEI-related complications (all in the CID group). Mortality was higher in patients aged more than 25 years old at alloSCT ($p = 0.029$). There was a trend for a higher mortality in the 24 patients with HCT-CI of at least 3 (1 year-OS 71% *vs*. 89% in the 54 patients with HCT-CI < 3, $p = 0.082$). Outcome was similar regardless of the donor, and *in vivo* T-cell depletion. Insufficient numbers of haploidentical transplants were performed to specifically comment on their use in this patient cohort.

Figure 2 shows the clinical course after transplantation. Among the 23 patients with CID transplanted following the development of IEI-related malignancy (**A**), 19 were in complete remission, one in partial remission and three had refractory disease at the time of transplantation. Three patients with XLP1 (*SH2D1A* deficiency) died more

than one year after transplant from TRM (two from GVHD and one from sepsis). Among patients transplanted for other indications (**B**), 42/55 (76%) had an active disease requiring treatment at time of transplantation (**Supplementary Table 9**). Complete or partial remission of these complications was achieved post alloSCT in all surviving CGD patients and the majority of surviving CID patients (n=21/27, 78%). Three patients died more than one year after transplant from chronic GVHD (n=2) or IEI-related complications (n=1) (**Supplementary Table 10**).

Causes of death in the transplanted patient group are detailed in **supplementary Table 11** and transplant-related morbidity is included in **supplementary Table 12**. Three CGD and eight CID patients experienced graft-failure, including partial engraftment at six months, requiring a second alloSCT in two patients, $CD34^+$ cell top-up in three and DLI in one. Among these 11 patients, five were alive and well at last follow-up. Grade III-IV acute GVHD occurred in 10 patients (two CGD and eight CID patients), of whom eight died. Three patients developed extensive chronic GVHD that led to death in two of them. Two CID patients developed an EBV-associated post-transplant lymphoproliferative disease, successfully treated by rituximab. Two CID patients developed a solid secondary malignancy, a neuroendocrine tumour 4.5 years post-transplant and a renal cancer 1.2 years post-transplant. Both patients are in complete remission at last review.

Outcome of transplanted versus matched non-transplanted patients

With a median follow-up of 4.8 years (IQR [2.5-7.2]), the projected 5-year DFS was 58% (95% CI, 46% to 75%) in the alloSCT group versus 33% (95% CI, 27% to 42%) in non-transplanted patients (p = 0.007) (**Figure 3A**). The estimated one-year TRM

was 13% (95% CI, 5% to 20%, **Figure 3B**). Projected 5-year cumulative incidence of mortality was higher in the alloSCT group (30%; 95% CI, 14% to 42% *vs*. 11%; 95% CI, 6% to 15% in non-transplanted patients; $p < 0.001$; **Figure 3D**). Since the effect of alloSCT on survival is time-dependent, we considered two periods for the multivariate analysis: the first period covering the first year after the procedure and the late period after the first year. The 5-year conditional OS (COS) was similar for 1-year survivors between both cohorts (84%; 95%CI, 71% to 100% *vs*. 90%; 95%CI, 86% to 95% in non-transplanted patients; **supplementary Figure 3**). Multivariable analysis revealed that alloSCT during the first period, invasive aspergillosis, autoimmunity and lymphoid malignancy were significantly associated with death (hazard ratio for alloSCT-first year, 5.43; 95% CI, 1.84 to 16.02; $p < 0.01$). Conversely, after the first year following the procedure, alloSCT was no longer associated with death (hazard ratio for alloSCT-late period, 1.49; 95% CI, 0.51 to 4.31; $p = 0.46$) (**Figure 4**). Therefore, the excess risk of alloSCT on OS was only significant during the first year post transplant.

In order to estimate the quality of life of non-transplanted versus transplanted IEI patients, we assessed the mean cumulative number of recurrent events (REs), examining first and subsequent events simultaneously, including both IEI-related and transplant-related morbidities. At one year, the mean cumulative number of REs was 0.42 in the alloSCT group versus 0.12 in non-transplanted patients. After four years, the number of REs was reversed between the two groups (for example, REs at eight years were 0.59 in transplanted patients compared to 1.08 in non-transplanted patients). Overall, beyond one-year post alloSCT, transplanted patients developed very few complications resulting in a plateau, while non-transplanted patients had a

continuously increased and progressive risk for severe IEI-related complications (**Figure 3C**). Multivariate analysis revealed that alloSCT during the first period, autoimmunity and lymphoid malignancy were significantly associated with recurrent events (hazard ratio for alloSCT-first year, 3.79; 95% CI, 2.29 to 6.26; $p < 0.01$). However, transplanted patients had significantly less recurrent events after the first year following the alloSCT procedure (hazard ratio for alloSCT-after first-year, 0.25; 95% CI, 0.1 to 0.6; $p < 0.01$) (**Figure 4**). Separate analyses for the CGD and CID groups are shown in **supplementary Figures 4 and 5**. As the number of patients labelled with a diagnosis of CVID, a complex, heterogeneous and incompletely understood disease entity, is much higher in the non-transplanted group, which may indicate that both intrinsic disease characteristics as well as disease manifestations were not properly matched between the alloSCT and non-alloSCT group, we performed sensitivity analysis by removing patients identified as CVID without breaking the matching. After their removal, 139 non-transplanted patients were compared to 72 transplanted patients with similar results in terms of OS, DFS and mean cumulative number of REs (**Supplementary Figure 6**), suggesting that patients with severe CVID had similar prognosis to patients with severe CID/IDS. These results were also similar in the subgroup of patients with CID (w/o CGD patients) and in sensitivity analysis by removing patients with CVID and/or lung involvement (data not shown).

DISCUSSION

We report the results of a large multicenter Franco-British study in which adults and adolescents over the age of 15 years undergoing alloSCT for IEI were paired and compared to matched non-transplanted controls collected from the French CEREDIH registry database. We show that alloSCT prevents the progressive morbidity associated with IEI in adults and is predicted to outweigh the negative impact of TRM.

There is ongoing debate about the role of alloSCT in older adolescents and adults with IEI, including specific indications for transplant and optimal timing. As prospective studies in such rare, heterogeneous diseases are difficult, we conducted a retrospective case-control study to explore the role of alloSCT. As expected, transplanted patients had severe IEI phenotypes; most had active complications at the time of alloSCT, high HCT-CI scores and at least an HCT-CI score of one in 86% of patients. As previously published, the most common indications for alloSCT were severe active colitis or invasive aspergillosis in CGD patients[22,23] and malignant lymphoproliferative disease[35], infection or complex immune dysregulation in CID patients[20,25]. Transplant-related mortality was 15% in CGD patients (3/20), which is consistent with previous reports[23] and a recently reported 2-year OS of 78% in a large retrospective EBMT study including 77 adult CGD patients[22]. In the CID patient group, the TRM was 19% (11/59). A retrospective study of patients with complex CVID who underwent alloSCT, reported higher mortality rates in 14 patients aged 18–50 years who had an OS of 57%, 21% graft failure and 21% severe GVHD[20]. On the contrary, excellent outcome has been recently reported in six CGD and 12 other

IEI patients aged 15 to 22 years, with an OS of 94%[11], in line with our previous study of RIC alloSCT in adult IEI patients reporting a 3-year OS of 85%[25]. A prospective clinical trial of a novel radiation free and serotherapy-free RIC, T-replete transplant platform in patients with IEI (including CID patients with various genetic diagnoses) showed encouraging preliminary results for the first 20 patients (including 10 aged over 18) with an 1-year OS at 90% and low incidence of GVHD (NCT02579967)[24]. The majority of recent data in adults with IEI has shown RIC alloSCT to be safe and effective, even in patients with high-risk pretransplant morbidity scores[11,20,22,24,25]. In contrast, a recent EBMT retrospective study analyzing outcome post alloSCT for adult IEI patients demonstrated no impact of conditioning intensity on OS or event-free survival[26]. In our study and as with other published studies, mortality was higher in patients aged at alloSCT of more than 25 years old and in those with higher comorbidity scores, suggesting that alloSCT should be undertaken earlier in the medical history of a patient with a severe IEI. Finally, alloSCT survivors experienced a continuous improvement with evidence of phenotype reversal over time, including those with mixed chimerism at last review.

To better define the role of alloSCT, we compared outcomes of transplanted versus non-transplanted matched patients. In our transplant group, serious events were limited to the first-year post-transplant, while non-transplanted patients continued to accrue serious complications over time. This is highlighted by the DFS and REs curves that demonstrate a linear increase in the number of serious events in non-transplanted patients. AlloSCT has the potential to cure the underlying IEI but carries an immediate risk of transplant-related mortality, which translated into lower short-term survival. However, short-term OS could not be compared without bias, as some

non-transplanted patients may have developed significant complications a long time before reaching the age at alloSCT while the transplant group has an additional risk of transplant-related death within the months after alloSCT. Our study has demonstrated a clear benefit for transplanted patients compared to non-transplanted controls, with improved DFS and reduced cumulative incidence of REs. Longer follow-up in future studies is required to determine the impact of alloSCT on survival.

Our study has several limitations, including those intrinsic to its retrospective design. In our matching strategy, we aimed to limit bias linked to treatment decades or heterogeneity of IEI subtypes, whilst not excluding large numbers of patients and depleting the pool of matched controls for these rare conditions. For the same reason, patients were matched to controls who had reached the same age as the transplanted index patient, and the time of analysis was calculated from the transplant age (randomization age for the controls) (**Supplementary Figure 1**). The degree of severity of the CID group was considered to avoid matching a patient with mild CVID to a patient with complex CVID or CID. The large group of CID patients was thus defined as having a similar phenotype based on the occurrence of autoimmune complications, lymphoproliferative disease or both. Selection of controls was blinded and performed by random sampling, from the CEREDIH register. Despite these precautions, the alloSCT cohort showed an increased incidence of infections. By contrast, non-transplanted patients had more pulmonary involvement. This may reflect selection bias prior to referral for alloSCT, which is impossible in this study to completely eradicate. Further, there may be a tendency to reclassify severe CVID patients referred for alloSCT as CID, leading to a seemingly CID-dominated transplant cohort and a CVID-rich control group. Nevertheless, there was no

difference in IEI-related complications in non-transplanted patients classified as CVID compared to other CID patients (IDS and LoCID) in keeping with the clinical overlap between complex CVID, IDS and LoCID (**supplementary table 4**). Moreover, sensitivity analyses performed by removing patients with CVID and/or with lung involvement showed similar survival outcomes. Taking into account these limitations, our data shows that transplanted patients had significantly better DFS than controls. We believe this is an important message. As in other studies, our findings highlight the need for improved immunological and genetic assessment of patients with severe or complex CVID.

The results of our study highlight the need for consensus recommendations on the timing of and indication for alloSCT in adult patients with severe IEI[7] and indeed, the most recent international published guidelines on alloSCT include a section on adult IEI patients[28]. In patients with CGD, complications increase as patients age justifying the discussion of alloSCT whenever a patient has a suitable donor. In patients with severe CID, the decision is more complex and is influenced by the type of CID, disease severity, comorbidities, and donor availability. Typically, there are 2 main categories of patients: (1) where the indication for alloSCT is clear (e.g. well-characterized gene defect with predictable poor prognosis and severe previous IEI-related complications) and the patients has an HCT-CI score between 0 and 2 and an appropriately matched donor; (2) where alloSCT is predicted to result in excessively high TRM (patients with an HCT-CI score of at least 3 and multiple IEI-associated complications at transplant) or is impossible due to the absence of a suitable donor[26]. In these patients, the individual benefit-risk balance should be carefully discussed with the patient and at a specialist multidisciplinary team (MDT) meeting. Proceeding

to alloSCT may be indicated depending on the severity of the underlying IEI. In all cases, recommendations need to be balanced by the availability of and response to potentially effective targeted therapies (such as abatacept in LRBA/CTLA-4 deficiency). Patients should be discussed at a specialist MDT meeting, with clinicians experienced in alloSCT for adult IEI patients. Work is in progress to validate the immune deficiency and immune dysregulation activity (IDDA) score[36] in predicting outcome following alloSCT in adults with IEI.

In summary, the findings from this study demonstrate that alloSCT in adolescents over 15 years of age and adults for CGD and CID can halt the otherwise progressive increase in IEI-related events and associated morbidity, which contribute to a worsening quality of life and increased hospital admissions. Continued advances in transplant-specific supportive care in specialist adult IEI transplant centers may further reduce the TRM and improve the applicability of alloSCT as a treatment strategy for adults with IEI.

Authorship contributions: MC, ECM, FS, NM, SB and TAF conceptualized, supervised the study and wrote the manuscript. MC, TAF provided data and data analysis. MA, OB, MC, NM, FS and JPJ performed statistical analysis. All authors, except MA and OB provided clinical care for the patients described. MC obtained fundings. All authors edited and approved the final version of the paper. MC, ECM, FS, NM, SB and TAF were responsible for the final version of the manuscript.

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FIGURE LEGENDS

Figure 1: Flow-chart

Transplanted patients were included in the study if they fulfilled the following criteria: (a) age at first alloSCT ≥ 15 years; (b) transplanted between January 2008 and December 2018; (c) underlying IEI diagnosis of CGD or CID. Matching criteria were (a) decade of birth; (b) age at last review greater than age at alloSCT; (c) one of two IEI categories (CGD *vs*. CID, including profound T-cell deficiency, CVID and IDS); (d) patients in the CID category were further matched by disease severity (including autoimmune/inflammatory manifestation and/or malignant lymphoproliferative disease), regardless of the date of this complication. A random draw without replacement was then performed to select up to three controls per index case.

Figure 2: Evolution of disease following alloSCT

A. Evolution of patients transplanted with previous lymphoproliferative disease, by status of malignancy at alloSCT. All patients had combined immune deficiency (n=22 patients). Two patients were alive in complete remission with mixed chimerism at last review.

B. Evolution of patients transplanted with no prior lymphoproliferative disease, by status of IEI-related complication at alloSCT. Patients had combined immune deficiency (CID, n=36 patients, light gray) or chronic granulomatous disease (CGD, n=20 patients, dark gray). Twelve patients were alive with mixed chimerism at last review, of whom six were in complete remission.

Arrows and circles indicate living patients and mixed chimerism respectively at last review. The letter A indicates subsequent alloSCT that occurred 5, 7 and 10 months after the first alloSCT.

Figure 3: Outcome of transplanted versus matched non-transplanted patients

(A) Kaplan-Meier estimated disease-free survival (DFS) for transplanted (red) and non-transplanted (blue) patients, **(B)** Cumulative incidence of transplant related mortality (TRM) for transplanted patients, **(C)** Mean cumulative number of recurrent events (REs) and **(D)** Cumulative incidence probability for death from all causes in transplanted (red) versus matched non-transplanted control (blue) patients. DFS was defined as time between baseline and IEI-related events (events defined as infection requiring hospitalization, severe autoimmune or inflammatory manifestation, malignancy) or death, whichever occurred first. For analysis of REs, an event was defined as an IEI-related severe complication (including infection requiring hospitalization, severe autoimmune or inflammatory manifestation, malignancy), as well as transplant-related severe events (including grade 3-4 acute GVHD and extensive chronic GVHD, graft failure, $CD34^{+}$ top-up, donor lymphocyte infusion, secondary malignancy, post-transplant lymphoproliferative disease, viral reactivations requiring systemic anti-viral or cellular therapy).

Figure 4: Cox multivariate analysis

Forest plots of the effects of alloSCT versus conservative treatment and identified risk factors. The effects are shown by proportional hazard risks for death and for recurrent events (REs), obtained by Cox proportional hazards regression.

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TABLES

Table 1: Comparisons of IEI-related complications in transplanted and matched non-transplanted patients with combined immune deficiency (CID).

Complications at baseline		All patients, n (%) (n=212)	No alloSCT, n (%) (n=153)	alloSCT, n (%) (n=59)	*p-value*
Infections					
	Bacterial infection	101 (48%)	60 (39%)	41 (69%)	***<0.001***
	*Viral infection**	32 (15%)	7 (5%)	25 (42%)	***<0.001***
	Parasitic infection	8 (4%)	2 (1%)	6 (10%)	***0.007***
	Invasive aspergillosis	11 (5%)	5 (3%)	6 (10%)	***0.042***
Autoimmune cytopenia					
	Autoimmune neutropenia	27 (14%)	19 (12%)	8 (18%)	*0.327*
	Autoimmune hemolytic anemia	47 (23%)	42 (27%)	5 (10%)	***0.011***
	Autoimmune thrombocytopenia	35 (17%)	28 (18%)	7 (12%)	*0.258*
Colitis		**43 (20%)**	**29 (19%)**	**14 (24%)**	*0.438*
Granuloma		**28 (13%)**	**21 (14%)**	**7 (12%)**	*0.72*
Liver involvement**		**27 (13%)**	**19 (12%)**	**8 (14%)**	*0.823*
Interstitial pulmonary involvement***		**25 (12%)**	**23 (15%)**	**2 (3%)**	***0.017***
Hemophagocytic syndrome		**14 (7%)**	**8 (5%)**	**6 (10%)**	*0.194*
Vasculitis		**6 (3%)**	**3 (2%)**	**3 (5%)**	*0.351*
Malignancy					
	Lymphoid proliferation	70 (33%)	48 (31%)	22 (37%)	*0.412*
	Myeloid malignancy	2 (1%)	1 (1%)	1 (2%)	*0.48*
	Solid cancer	11 (5%)	8 (5%)	3 (5%)	*1*

*Viral infections included extensive warts, EBV-associated ulcers, complicated VZV infection, HPV-CIN, EBV viraemia; and varicella without complication, herpes virus and HPV-CIN in non-transplanted patient; **Liver involvement included nodular regenerative hyperplasia, sclerosing cholangitis, one patient with hepatitis T-cell infiltration and another with EBV-hepatitis; ***Lung involvement included 9/23 non-transplanted patients with CTLA-4/LRBA deficiency.

Table 2: Comparisons of IEI-related complications in transplanted and matched non-transplanted patients with chronic granulomatous disease (CGD).

Complications at baseline		All patients, n (%) (n=69)	No alloSCT, n (%) (n=49)	alloSCT, n (%) (n=20)	*p-value*
Infections					
	Bacterial infection	56 (81%)	37 (76%)	19 (95%)	*0.09*
	Viral infection	1 (1%)	1 (2%)	0 (0%)	*1*
	Fungal infection	33 (48%)	22 (45%)	11 (55%)	*0.446*
	Invasive aspergillosis	28 (41%)	19 (39%)	9 (45%)	*0.633*
Autoimmune cytopenia		**1 (1%)**	**1 (2%)**	**0 (0%)**	*1*
Colitis		**29 (42%)**	**19 (39%)**	**10 (50%)**	*0.391*
Granuloma		**20 (29%)**	**14 (29%)**	**6 (30%)**	*0.906*
Liver Involvement*		**4 (6%)**	**4 (8%)**	**0 (0%)**	*0.315*
Interstitial Pulmonary Involvement		**8 (12%)**	**7 (14%)**	**1 (5%)**	*0.422*

Hemophagocytic syndrome	**1 (1%)**	**1 (2%)**	**0 (0%)**	*1*
Lymphoid proliferation	**1 (1%)**	**1 (2%)**	**0 (0%)**	*1*

*Liver involvement included hepatic fibrosis in two patients and granulomatous hepatitis in two patients.

Table 3: Indications for alloSCT.

	All transplanted patients, n (%) (n=79)	CGD, n (%) (n=20)	CID, n (%) (n=59)
Preemptive	1 (1%)	0 (0%)	1 (2%)
Infection	10 (13%)	3 (15%)	7 (12%)
Invasive aspergillosis	9 (12%)	9 (45%)	0 (0%)
Malignancy*	23 (29%)	0 (0%)	23 (40%)
AI neutropenia	8 (10%)	0 (0%)	8 (14%)
AI hemolytic anemia	1 (1%)	0 (0%)	1 (2%)
Colitis**	15 (19%)	8 (40%)	7 (12%)
Liver involvement***	7 (9%)	0 (0%)	7 (12%)
Hemophagocytic syndrome	2 (3%)	0 (0%)	2 (3%)
Vasculitis	2 (3%)	0 (0%)	2 (3%)
NA	*1*	*0*	*1*

*Malignant lymphoproliferative disease (except one patient with Bowen disease); **Crohn-like colitis (except one patient with Cryptosporidium associated-enteropathy); ***Nodular regenerative hyperplasia, sclerosing cholangitis, one patient had hepatitis T-cell infiltration and another had EBV-associated hepatitis; AI: autoimmune; NA: non available.

Table 4: Characteristics of allogeneic stem cell transplantation procedure.

		All patients, n (%) (n=79)	CGD, n (%) (n=20)	CID, n (%) (n=59)
Donor	MRD	30 (38%)	7 (35%)	23 (39%)
	MMRD	4 (5%)	0 (0%)	4 (7%)
	MMUD	12 (15%)	3 (15%)	9 (15%)
	MUD	33 (42%)	10 (50%)	23 (39%)
Stem cell source	BM	35 (44%)	13 (65%)	22 (37%)
	PBSC	44 (56%)	7 (35%)	37 (63%)
Conditioning intensity	Full	33 (42%)	5 (25%)	28 (47%)
	Reduced	46 (58%)	15 (75%)	31 (53%)
HCT-CI score	0	10 (13%)	1 (5%)	9 (16%)
	1-2	44 (56%)	13 (65%)	31 (53%)
	≥3	24 (31%)	6 (30%)	18 (31%)
	NA	*1*	*0*	*1*
Regimen	Flu/Mel	19 (24%)	0 (0%)	19 (32%)
	Flu/Bu (≤9.6 mg/Kg)	21 (27%)	15 (75%)	6 (10%)
	Flu/Bu (>9.6 mg/Kg)	26 (33%)	5 (15%)	21 (36%)
	Baltimore regimen	4 (5%)	0 (0%)	4 (8%)
	Flu/Treosulfan	2 (3%)	0 (0%)	2 (3%)

	Flu/Bu/Thiotepa	2 (3%)	0 (0%)	2 (3%)
	CCP/Bu	1 (1%)	0 (0%)	1 (2%)
	CCP/TBI (12Gy)	2 (3%)	0 (0%)	2 (3%)
	CCP/Flu	1 (1%)	0 (0%)	1 (2%)
	Flu/TBI (2Gy)	1 (1%)	0 (0%)	1 (2%)
***In-vivo* T-cell depletion**	Alemtuzumab	36 (46%)	9 (45%)	27 (46%)
	ATG	29 (37%)	11 (55%)	18 (31%)
GVHD prophylaxis	Cyclosporine	75 (95%)	19 (95%)	56 (95%)
	MMF	56 (71%)	16 (80%)	40 (68%)
	Methotrexate	15 (19%)	2 (10%)	13 (22%)
	Post-transplant cyclophosphamide	4 (5%)	0 (0%)	4 (7%)

MRD: matched-related donor; MMRD: mismatched- related donor; MMUD: mismatched unrelated donor; MUD: matched unrelated donor; CGD: chronic granulomatous disease; CID: combined immune deficiency; BM: bone marrow; PBSC: peripheral blood stem cells; TBI: total body irradiation; NA: not available; ATG: anti-thymocyte globulin; MMF: mycophenolate mofetil; Flu: fludarabine; Mel: melphalan; Bu: busulfan; CCP: cyclophosphamide; TBI: total body irradiation

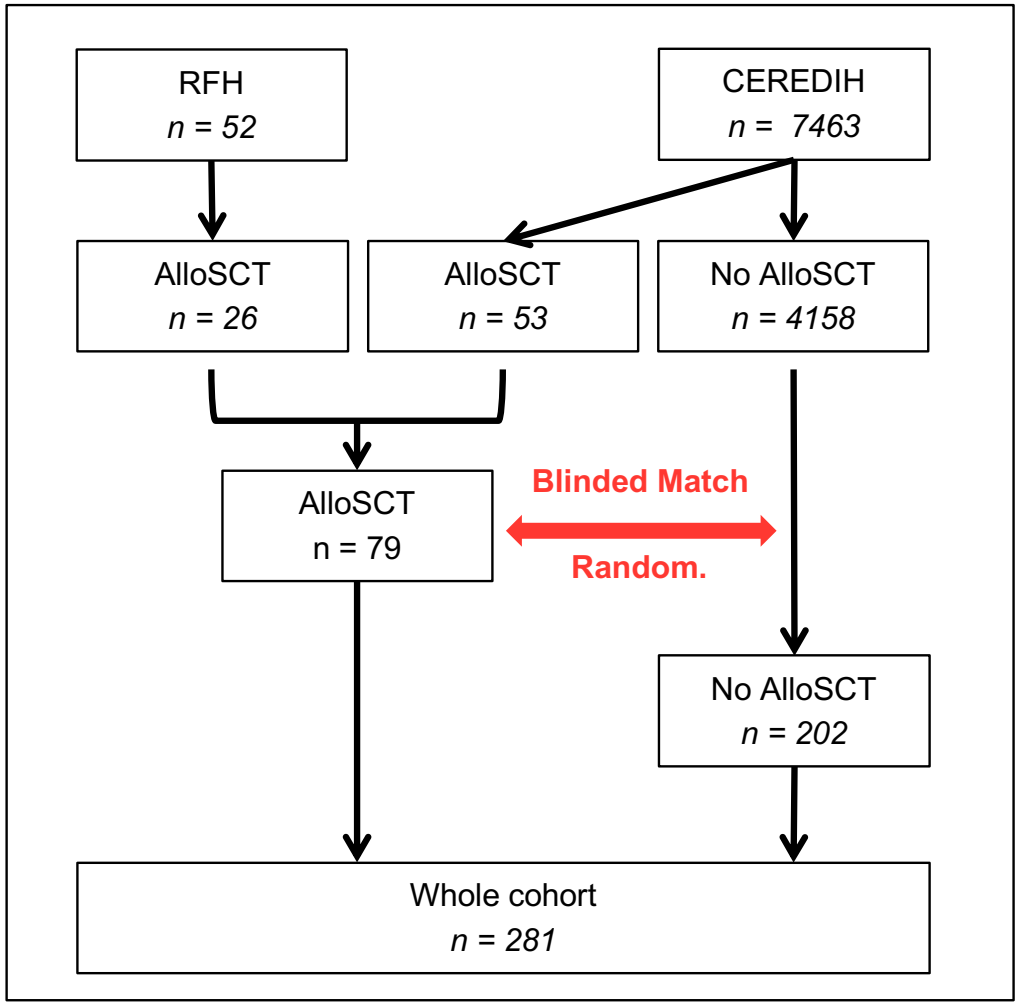

Figure 1: Flow-chart

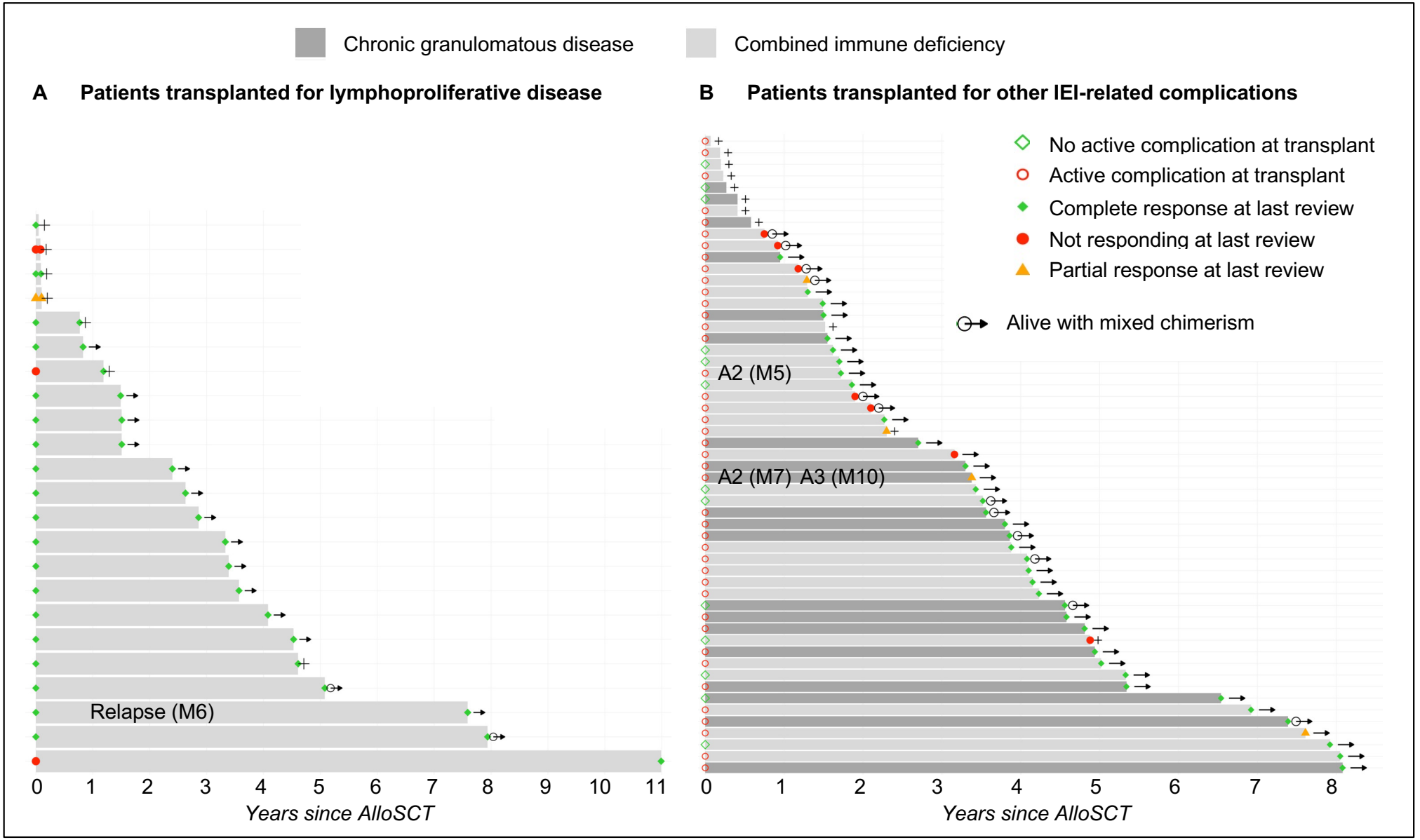

Figure 2: Evolution after alloSCT in patients with previous lymphoproliferative disease (A) and with other IEI-related complication (B)

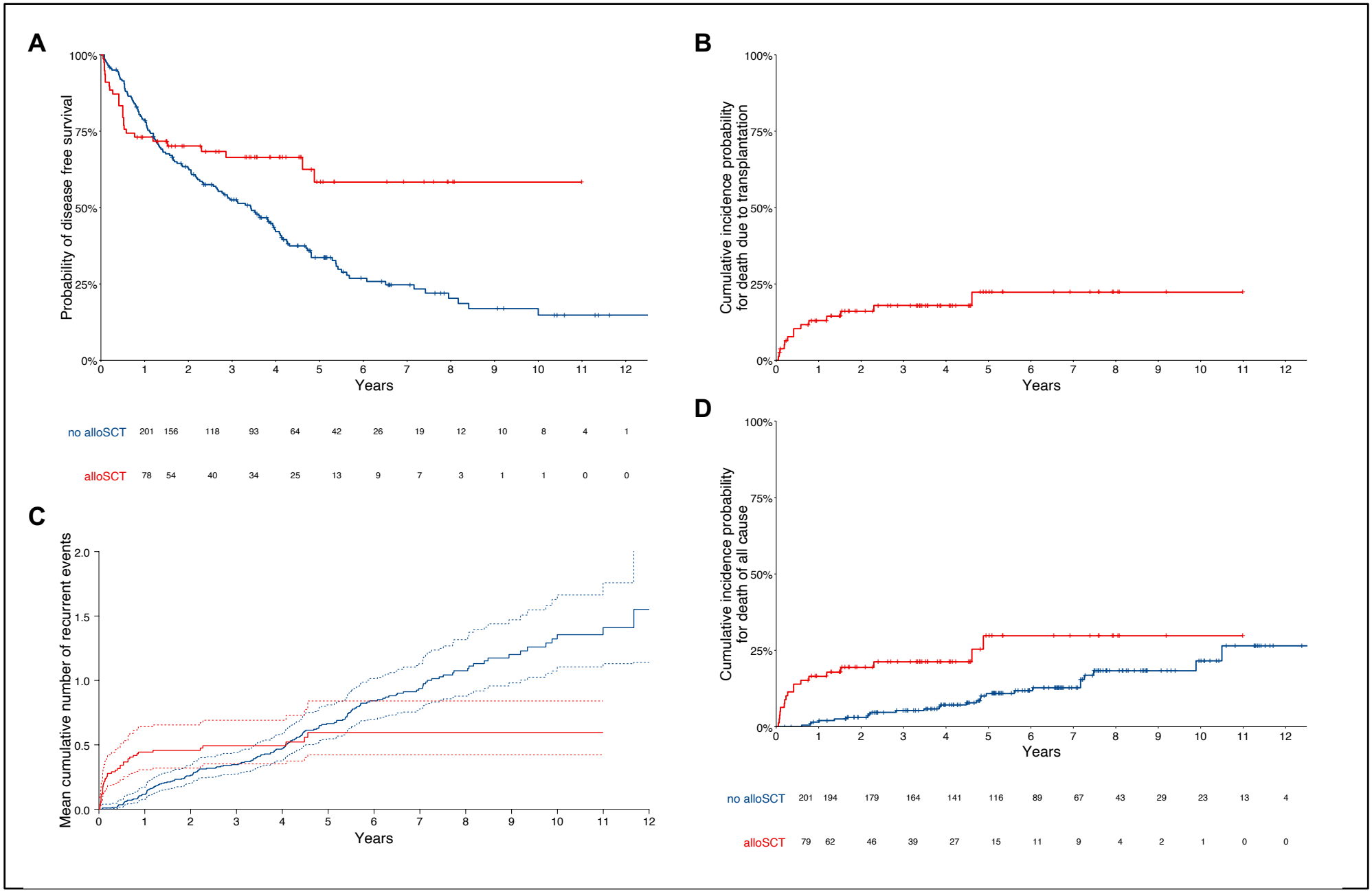

Figure 3: Outcome of transplanted versus matched non-transplanted patients

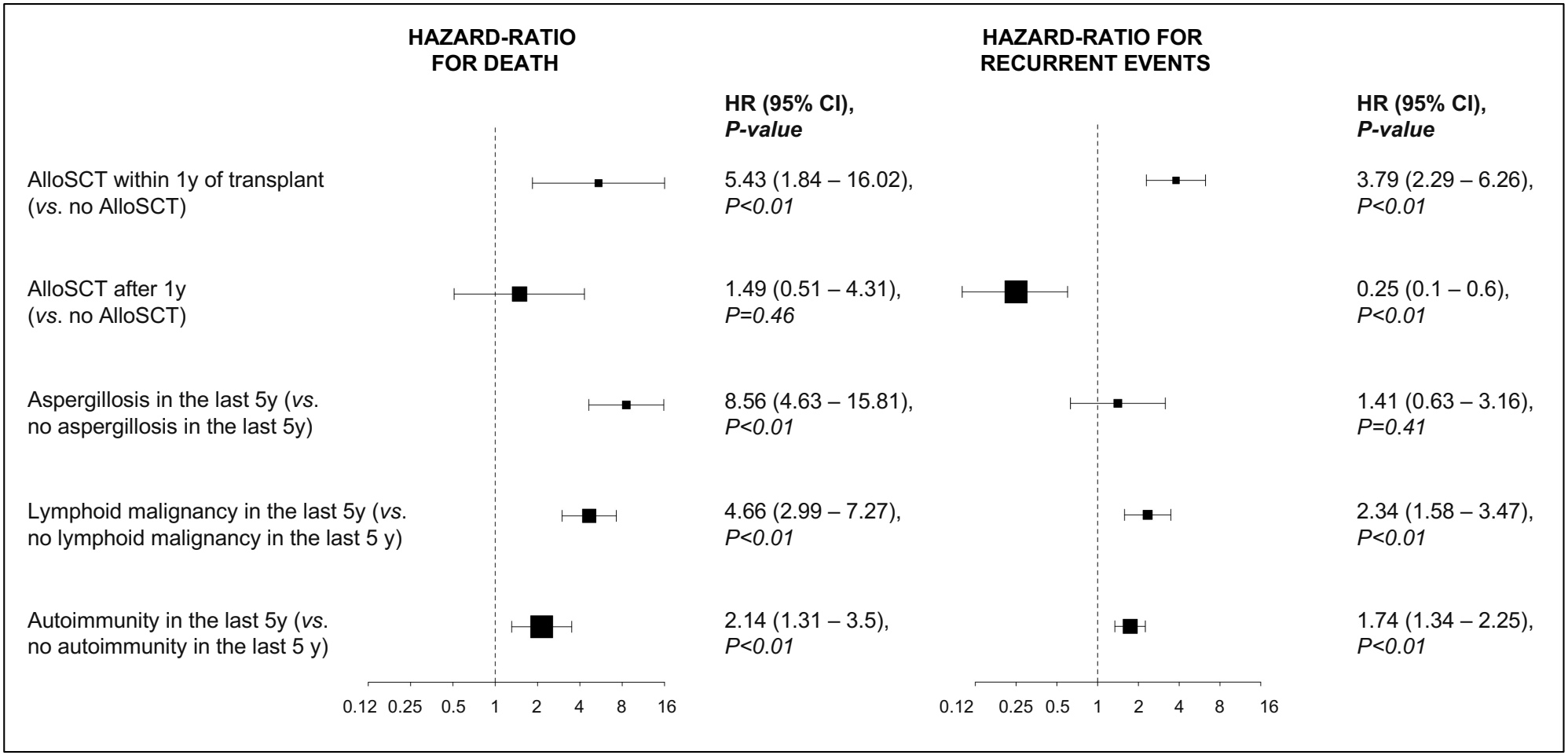

Figure 4: Cox multivariate analysis