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Hematopoietic stem cell transplantation for adolescents and adults with inborn errors of immunity, an EBMT IEWP study

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Abstract:
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This large retrospective, multicenter HSCT outcome study reports on 329 IEI patients (age range 15-62.5 years at HSCT). Patients underwent first HSCT between 2000 and 2019. Primary endpoints were overall survival (OS) and event-free survival (EFS). We also evaluated the influence of IEI-subgroup and IEI-specific risk factors at HSCT, including infections, bronchiectasis, colitis, malignancy, inflammatory lung disease, splenectomy, hepatic dysfunction and systemic immunosuppression.

At a median follow-up of 44.3 months, the estimated OS at 1 and 5 years post-HSCT for all patients was 78% and 71% and EFS was 65% and 62%, respectively, with low rates of severe acute (8%) or extensive chronic (7%) GVHD. On univariate analysis, OS and EFS were inferior in patients with primary antibody deficiency, bronchiectasis, prior splenectomy, hepatic comorbidity, and with higher HCT-CI scores. On multivariable analysis EFS was inferior in those with a higher number of IEI-associated complications. Neither age nor donor had a significant effect on OS or EFS.

We have identified age-independent risk factors for adverse outcome, providing much needed evidence to identify which patients are most likely to benefit from HSCT.

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Conflict of interest: COI declared - see note

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Hematopoietic stem cell transplantation for adolescents and adults with inborn errors of immunity, an EBMT IEWP study

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KEY POINTS

This is the largest cohort of transplanted adolescent and adult IEI patients studied to date, detailing outcomes for 329 patients.

This study demonstrates OS and EFS and identifies adverse risk factors to help identify patients most likely to benefit from HSCT.

ABSTRACT

Allogeneic hematopoietic stem cell transplantation (HSCT) is the gold standard curative therapy for infants and children with many inborn errors of immunity (IEI), but adolescents and adults with IEI are rarely referred for transplant. Lack of published HSCT outcome data outside small, single-center studies and perceived high risk of transplant related mortality have delayed the adoption of HSCT for IEI patients presenting or developing significant organ damage later in life.

This large retrospective, multicenter HSCT outcome study reports on 329 IEI patients (age range 15-62.5 years at HSCT). Patients underwent first HSCT between 2000 and 2019. Primary endpoints were overall survival (OS) and event-free survival (EFS). We also evaluated the influence of IEI-subgroup and IEI-specific risk factors at HSCT, including infections, bronchiectasis, colitis, malignancy, inflammatory lung disease, splenectomy, hepatic dysfunction and systemic immunosuppression.

At a median follow-up of 44.3 months, the estimated OS at 1 and 5 years post-HSCT for all patients was 78% and 71% and EFS was 65% and 62%, respectively, with low rates of severe acute (8%) or extensive chronic (7%) GVHD. On univariate analysis, OS and EFS were inferior in patients with primary antibody deficiency, bronchiectasis, prior splenectomy, hepatic comorbidity, and with higher HCT-CI scores. On multivariable analysis EFS was inferior in those with a higher number of IEI-associated complications. Neither age nor donor had a significant effect on OS or EFS.

We have identified age-independent risk factors for adverse outcome, providing much needed evidence to identify which patients are most likely to benefit from HSCT.

INTRODUCTION

Inborn errors of immunity (IEI) are a wide group of genetically determined, rare and complex lifelong diseases [1]. The majority are characterized by severe infection and immune dysregulation including autoimmunity, autoinflammation and an increased risk of malignancy. In children with IEI, survival and cure rates after allogeneic hematopoietic stem cell transplantation (HSCT) are now excellent, particularly in the absence of organ damage and/or infectious burden at transplant [2-5]. Consequently, there is a steady increase in HSCT activity for these patients [6].

HSCT for older adolescents and adults with IEI was uncommon until recently, mainly due to perceived high risks of transplant related mortality (TRM) and was reserved as a last resort for patients with excessive morbidity [7-9]. Indeed, initial publications on HSCT for adults with common variable immunodeficiency (CVID) reported disappointing survival rates of approximately 50% in patients who had acquired significant organ damage pre-HSCT [10]. In contrast, adolescents and very young adults with limited IEI related morbidity can expect excellent outcomes very similar to their pediatric counterparts [11,12]. Moreover, when using reduced toxicity conditioning regimens in specialized centers, even older adult IEI patients with advanced disease can expect good survival probabilities and improvement of quality of life after HSCT [12,13]. Consequently, adults with IEI have recently been added to the list of indications for HSCT by EBMT and ASTCT [14-16]. To date all published retrospective [4, 10-12] and prospective [13, 22] studies on HSCT outcomes in adults with IEI taken together report on $<$150 patients.

In children with genetically confirmed IEI known to have a poor prognosis with conservative therapy alone, the role of HSCT is usually well defined and supported by clear evidence for transplant efficacy [4]. However, the decision to proceed to HSCT is challenging in older patients who may have a milder disease course during childhood or late onset presentation, in diseases with variable phenotypic severity/penetrance or poorly documented natural history, and in the absence of a genetic diagnosis [17]. Further complexity is added by issues including fertility and family planning, psychosocial wellbeing, access to targeted therapies, and the need for careful donor and conditioning regimen selection, necessitating specialized interdisciplinary care [9,18].

The hematopoietic cell transplant comorbidity index (HCT-CI) score has been validated as a predictive marker for survival in patients with non-malignant diseases [19], but IEI-specific risk factors still need to be identified for this group. We undertook a multicenter retrospective analysis of the EBMT registry to report HSCT outcomes for adolescents and adults with IEI in the last two decades. Overall and event-free survival were reported and IEI-specific risk factors for poor outcomes were identified, to aid patient selection for HSCT.

PATIENTS AND METHODS

Data source

This international, multicenter retrospective analysis (study number 8427018) was performed on behalf of the European Society for Blood and Marrow Transplantation (EBMT) and European Society for Immunodeficiencies (ESID) Inborn Errors Working Party (IEWP). EBMT centers commit to obtain informed consent according to the local regulations when reporting pseudonymised data to the EBMT. The EBMT registry provided HSCT data, and a study specific questionnaire was completed by the study centers.

Study Participants and transplant procedures

Eligibility criteria included age $\geq$ 15 years at HSCT, confirmed clinical and/or genetic diagnosis of IEI and first HSCT between 2000 and 2019. The study cohort included 329 patients from 51 centers. Basic demographic data included age, sex, IEI subgroup, genetic diagnosis, age at diagnosis, age at HSCT, time from diagnosis to HSCT, HCT-CI score [20] and year of HSCT. Transplant specific demographics included donor type, cell source, conditioning intensity, use of serotherapy and donor/recipient CMV serostatus.

Chimerism analysis

Chimerism samples were processed as per local center protocols and included either whole blood or lineage-specific analysis.

Definitions

Neutrophil and platelet recovery were defined as the first of 3 consecutive days with an absolute neutrophil count >0.5 x 10^9/L, or an unsupported platelet count >20 x 10^9/L. Graft failure was defined as the absence of neutrophil recovery on day +28 or donor chimerism in peripheral blood <5% beyond day +28 [21].

Grading of acute and chronic GVHD was performed according to modified Seattle criteria and NIH consensus standards, where available [22]. Hepatic dysfunction at HSCT was graded as either mild or moderate/severe by the reporting physician.

In this study conditioning intensity was defined as follows: myeloablative (MA): regimens containing busulfan doses >12mg/kg and/or total AUC >80.000 ng*h/ml; fludarabine plus melphalan plus either treosulfan or BCNU; reduced toxicity conditioning (RTC): busulfan ≤12mg/kg or AUC ≤80.000 ng*h/ml; treosulfan-based unless combined with melphalan; fludarabine and melphalan; and non-myeloablative (NMA): fludarabine plus cyclophosphamide; TBI 2Gy plus fludarabine.

To facilitate outcome analysis based on IEI subgroups three groups were established based on the most recent IUIS classification of IEI [1]: Phagocyte disorders/innate (PD); Combined immunodeficiencies (CID); and Predominantly antibody defects (PAD). For detailed information of underlying diagnoses, see ***Supplementary Data Table 1*.**

Statistical analysis

Patient and transplant characteristics were expressed as the number and percentage of the group for categorical variables and median with ranges for continuous variables. The time origin for time-to-event analysis was first HSCT, and patients alive without an event after transplant were censored at last follow-up or time of data extraction.

Primary endpoints were overall survival (OS), where an event was defined as death of any cause and event-free survival (EFS), where an event was defined as graft failure (GF), moderate to severe cGVHD or death, whichever happened first.

Secondary endpoints evaluated the influence on OS and EFS of the IEI subgroup, HCT-CI score, age at HSCT and additional IEI-specific risk factors at the time of HSCT, including infections, low BMI (<18), bronchiectasis, colitis, malignancy, granulomatous lymphocytic inflammatory lung disease (GLILD), splenectomy, hepatic dysfunction, autoimmunity and systemic immunosuppressive therapy. Peripheral blood chimerism, requirement for immunoglobulin replacement therapy (IgRT), performance status, attendance of work or school and conception at last follow-up were also documented.

OS and EFS were estimated using the Kaplan-Meier product limit estimation method, and differences in subgroups were assessed by the Log-Rank test. Median follow-up was determined using the reverse Kaplan-Meier method. Competing risks analyses were applied to estimate the incidences of acute grade II-IV GvHD and limited and extensive chronic GvHD (cGvHD), by day 100 and one and two years respectively. The competing events were second transplant, graft failure or non-engraftment and death. Subgroup differences in cumulative incidences were assessed using Gray's test. Competing risks analyses were also applied to estimate incidences of neutrophil engraftment and platelet recovery, each with death as the competing event. Multivariable Cox regression was applied to investigate the simultaneous impact of multiple covariates on outcomes, when a sufficient number of patients and subsequent events were available. For OS and EFS, hazard ratios are provided. Both models use the same covariate structure: IEI Subgroup (PAD, PD versus CID), number of pre-HSCT IEI complications (1 complication, ≥2 complications versus no complications), age at HSCT (Hazard Ratio, HR per decade increase in age), Sorror score (HCT-CI 1-2, HCT-CI >2 versus HCT-CI 0) and conditioning intensity (MA, RTC versus NMA). Significance of individual HR was determined by means of the Wald test. Likelihood ratio tests were performed to determine overall significance of covariates. Based on the number of events there were a limited number of covariates which could be tested; these were selected based on clinical relevance.

All survival estimates and HR are reported with corresponding 95% confidence intervals in parentheses. All p-values were two-sided and $p<0.05$ was considered significant. Statistical analyses were performed in R version 3.6.0 (R Development Core Team, Vienna, Austria), using packages 'survival', 'prodlim' and 'cmprsk'.

RESULTS

Patient and HSCT characteristics

329 patients (223 males and 106 females) were included in this study and detailed patient demographics are shown in ***Table 1***.

The median age at HSCT was 18.4 years (IQR 16.6-22.8; range 15-62.5), with a median age at clinical diagnosis of 13 years (3.6-17.2; 0-62.1) and median time from clinical diagnosis to HSCT of 5.3 years months (1.1-15.8; 0-39.3). Median age at last follow-up for the whole cohort was 23.2 years (19.5-28.3; 15.2-62.6).

Underlying IEI diagnoses (genetically and/or clinically confirmed) were grouped into CID (49.5%), PD (38.6%) and PAD (11.9%) with further details shown in ***Supplementary Data Table 1***. Within the CID subgroup (n=163), the most frequent diagnoses were genetically undefined CID (n=37), HLH (n=23), CD40L Deficiency (n=14), WAS (n=13) and DOCK8 Deficiency (n=12). Within the PD subgroup, the most frequent diagnoses were CGD (n=83), GATA2 Deficiency (n=25) and SCN (n=12). The PAD subgroup comprised 27 patients with CVID, 9 with APDS and 3 with XLA. Overall, the underlying disease remained genetically undefined in a total of 63 patients (19.1%, 37 CID and 26 PAD) at the time of writing.

IEI-related complications present at or immediately prior to HSCT are described in ***Table 1***. Most common were: infection (52% of whole cohort); bronchiectasis (26.5%); colitis or protracted diarrhoea (27.0%), malignancy (19.1%); GLILD (13.8%); hepatic comorbidity (13.1%) and prior splenectomy (9.5%).

35.2% of the cohort were on systemic immunomodulatory therapies immediately prior to HSCT for autoimmunity or inflammatory IEI-related complications. These included 32.5% of the CID subgroup, 48.7% of the PAD subgroup, and 31.5% of the PD subgroup. Details of immunomodulatory therapies are given in ***Supplementary Data Table 2***. For those patients (19.1% of whole cohort) with a documented malignancy prior to HSCT, 56.9% were in remission at the time of HSCT. Details of malignant diagnoses are given in ***Supplementary Data Table 3***.

One third (33%) of the total cohort had no active IEI-related complications at the time of HSCT, 36.3% had one complication and 30.8% of patients had two or more complications. Reflecting the co-morbidities associated with IEI, patients in our cohort had HCT-CI scores of 0, 1-2, 3-4 or $\geq$4 in 27.6%, 39.8%, 18.3% and 14.3%, respectively (***Table 1***). Some important differences in IEI-related complications were observed between IEI subgroups. Hepatic comorbidity was observed more frequently in patients with PAD (19.4% mild, 5.6% moderate/severe) than in patients with CID (8.1% mild, 8.1% moderate/severe) and PD (3.8% mild, 1% moderate/severe), p=0.003. Splenectomy prior to HSCT was observed more frequently in patients with CID (15.8%) and PAD (11.4%) than in patients with PD (0.8%), p=<0.001. Bronchiectasis at HSCT was observed more frequently in patients with PAD (43.2%) than in patients with CID (26.5%) and PD (21.6%), p=0.032 (***Table 2***).

Transplant characteristics are described in detail in ***Table 3***. Most patients underwent matched or mismatched unrelated donor transplants (n=200, 62.1%).

Engraftment and graft failure

Median time to neutrophil engraftment was 18 days (95% CI: 17-19 days), with 87% (83-91%) of patients achieving neutrophil engraftment by 28 days. The median time to platelet recovery was 18 days (17-20), with 72% (66-77%) patients achieving platelet engraftment by 28 days.

Graft failure (GF) was observed in 28 patients (8%). These were categorized as primary in 12 and secondary in 16. For those patients developing GF (n=28), this was not related to IEI subgroups (p = 0.204, data not shown). The incidence of primary and secondary graft failure, combined as a single endpoint (with second transplant and death as competing events) was not influenced by IEI subgroup, donor, stem cell source or conditioning intensity, p=0.15, p=0.5, p=0.4 and p=0.07, respectively (***Supplementary Data Table 4***).

Survival

Estimated OS and EFS at 6 months, 1 year and 5 years for the whole cohort and IEI subgroups are shown in ***Table 4***.

Overall survival (OS)

237 patients were alive at last follow up (median 44.3 months post-HSCT) with an estimated OS at 1 year and 5 years post-HSCT of 78% and 71%, respectively, for the whole cohort (***Figure 1A***).

In univariate analysis, OS at 1 year and 5 years post-HSCT was significantly influenced by IEI subgroup being 93% and 78% for PD (n=127); 76% and 68% for CID (n=163), and 59% at both time points for PAD (n=39), p=0.007 (***Figure 1B***). The presence (n=126) or absence (n=37) of a genetic diagnosis in the CID group had no impact on OS, p=0.5 (data not shown).

The presence of various individual IEI-related complications at the time of HSCT were shown to adversely affect OS at both 1 and 5 years post-HSCT including bronchiectasis (p=0.026), prior splenectomy (p=0.008), and liver disease (p=0.017) as shown in ***Figures 1C-E***. We assessed the impact of the number of IEI associated complications at the time of HSCT on OS, including bronchiectasis, colitis, malignancy, GLILD, hepatic comorbidity, and splenectomy. OS was significantly worse for patients with two or more complications at the time of HSCT, p=0.02 (***Figure 1F***).

As in other adult HSCT cohorts higher pre-transplant HCT-CI scores (≥2) identified patients with inferior OS at 1 and 5 years post-HSCT, p=0.01 (***Figure 1G***). Finally, the year of transplant significantly influenced outcome and better OS was observed for those transplanted in 2014 or later compared to those transplanted before that, p=0.017 (***Figure 1H***).

Neither age at HSCT nor donor type significantly influenced OS at 1 and 5 years post-HSCT, p=0.177 and p=0.5, respectively (***Figures 1L, J***), although there was a trend for better OS in the younger patients. Univariate analysis for the whole cohort identified other factors that did not significantly impact OS, including conditioning intensity (p=0.6), pre-HSCT infection (p=0.2), active colitis at HSCT (p=0.6), pre-HSCT malignancy (p=0.8), and GLILD (p=0.16), as shown in ***Supplementary Figure 1***. Neither prior immunosuppressive therapy nor remission status of malignancy (where present) influenced OS (data not shown).

Subsequent multivariate analysis identified no risk factors statistically significant for OS, but IEI subgroup and number of IEI complications had a trend to significance (***Table 5A***).

Event free survival (EFS)

Event free survival for the whole cohort at 1 and 5 years was 65% and 62%, respectively (***Figure 2A***) and was also affected by IEI subgroup being 72% and 69% for PD (n=123); 64% and 58% for CID (n=157) and 51% at both time points for PAD (n=39), p=0.023 (***Figure 2B***). Again, no impact of a genetic diagnosis was seen within the CID group, p>0.99 (data not shown). The presence of bronchiectasis, prior splenectomy and hepatic comorbidity at HSCT adversely affected EFS at both 1 and 5 years post-HSCT, p=0.021, p=0.033 and p=0.01 respectively (***Figures 2C-E***). EFS was also influenced by the number of IEI associated risk factors present at HSCT, p=0.029 (***Figure 2F***).

Neither the pre-transplant HCT-CI score, p=0.168 (***Figure 2G***); the era of transplant p=0.108 (***Figure 2H***); age at HSCT, p=0.4 (***Figure 2I***); donor type, p=0.9 (***Figure 2J***); prior immunosuppressive therapy (data not shown) or remission status of malignancy, where present, had a significant influence on EFS (data not shown).

Subsequent multivariable analysis confirmed only the number of IEI-associated complications at HSCT as a significant risk factor for EFS (p=0.05), as shown in ***Table 5B***.

Overall and event free survival analysis within IEI subgroups

In patients with CID (n=162) the presence of bronchiectasis and the number of IEI-associated complications at HSCT adversely affected OS (p=0.033 and p=0.009, respectively), while GLILD and number of IEI-associated complications adversely affected EFS (p=0.018 and p=0.038, respectively). For patients with PD (n=125) only bronchiectasis adversely affected OS and EFS, p=0.008. Despite small numbers, in PAD patients (n=36) both OS and EFS were significantly influenced by hepatic comorbidity and age at HSCT, p=0.003 and p=0.005, respectively (***Suppl Data Figure 2***).

Graft versus host disease

In keeping with the frequent use of serotherapy, the cumulative incidence of grades II-IV aGVHD was low at 22%, with only 8% patients developing grade III-IV aGVHD (***Figure 3A***). The cumulative incidence of extensive cGVHD was 7%. The incidence of combined limited and extensive GVHD was 16% at 1 year and 19% at 5 years post-HSCT (***Figure 3B***). Notably, IEI subgroup had no impact on rates of acute or chronic GVHD (***Suppl Data Table 5***). As expected, the absence of serotherapy increased the risk of grades II-IV aGVHD (p=0.039).

Chimerism

Either whole blood (WB) or lineage specific peripheral blood chimerism was available at last follow-up for a total of 154 patients.

For those with only whole blood chimerism results (n=85), rates of >95% donor, 50-95% donor, 5-50% donor and <5% donor chimerism were 95.3%, 2.4%, 2.4% and 0% respectively. Lineage-specific T cell chimerism (n=154) and myeloid chimerism (n=142) results at last follow-up were also available, with rates of >95% donor, 50-95% donor, 2-50% donor and <5% donor T cell chimerism of 66.9%, 22.7%, 9.1% and 1.3% respectively and myeloid chimerism of 81.7%, 9.9%, 6.3% and 2.1% respectively (***Figure 4***).

When stratified by IEI subgroup, no differences were observed between rates of full donor chimerism at 1 year post HSCT and at last follow-up (data not shown).

Immune reconstitution

Total lymphocytes and lymphocyte subsets, and the requirement for immunoglobulin replacement therapy (IGRT) at 2 years post HSCT (n=225) or at last assessment (n=329) are shown in ***Table 6***. Of note, at 2 years post HSCT 24.2% of patients were receiving IgRT and median lymphocyte subset counts were within the normal adult range.

Status at last follow up and causes of death

237 patients (72% of total cohort) were alive at last follow-up at a median of 44.3 months post-HSCT. Performance status was available for 186 patients (78.5% of surviving patients) with 91.9% patients reporting performance status (Lansky or Karnofsky) of 90% or greater. Accordingly, 87.3% of patients were attending school, higher education or were employed (data not shown).

Limited data on post-HSCT fertility was available. A total of 16 patients reported conception (for themselves or their partner) following HSCT. Of those, 12 conceptions resulted in a live birth, 1 unwanted pregnancy was interrupted, for 3 no data was available and there was 1 stillbirth/miscarriage.

For those 91 patients who died within the 5-year follow-up period, causes of death was transplant related mortality (TRM) in 73 (81.1%), recurrence of IEI (or IEI-related complication) in 11 (12.2%), other in 6 (6.7%) and not available in 1 (1.1%).

DISCUSSION

This important, timely study reports detailed outcomes following HSCT for the largest cohort to date of IEI patients aged 15 years or more at transplant. As 75% patients in this cohort were transplanted after 2011, it reflects contemporary transplant practice and supportive care. Until now, published HSCT outcome data in this rare patient group have been limited to single-center adult studies [11,12], or larger, predominantly pediatric studies including small numbers of older patients [3,4,5,23].

Older IEI patients referred for HSCT have usually developed disease-associated complications such as opportunistic infections, autoimmunity, autoinflammation, organ damage, and/or malignancies. Reflecting this, 72.4% of our cohort had HCT-CI scores of 1 or greater at HSCT, including 32.6% with an HCT-CI ≥3. A previous study validating the HCT-CI score in 796 immunodeficiency patients was a much lower risk cohort, with a median age at HSCT of 9 years and only 37.5% had an HCT-CI score of 1 of greater, including 15.7% with a score ≥3. Over 50% of our cohort had active IEI-related complications at HSCT, as currently it is much less common for asymptomatic adults with a genetic diagnosis of IEI (with or without family history) to be referred for consideration of HSCT, unless there is clear evidence of poor clinical outcomes in adulthood [18,24].

IEI related factors, which adversely affected outcomes, were bronchiectasis, prior splenectomy, hepatic comorbidity and cumulative number of IEI-related complications at HSCT. These were all more important than patient age, donor or conditioning intensity, suggesting that older age *per se* does not adversely affect HSCT outcome in carefully selected patients. Notably, hepatic comorbidity and bronchiectasis were more frequently seen in patients with PAD, particularly those with complex CVID, which may contribute to poorer outcomes observed in these patients. Our data strongly support the notion that HSCT should be considered for adult patients prior to development of significant end organ complications, specifically impairment of hepatic and pulmonary function, and that availability of an HLA-matched donor matters less, given the equally good outcomes achieved with 9/10 MUD and MMRD in this cohort. This is relevant for IEI patients, where chances of identifying suitable matched related donors are reduced by the genetic origin of the disease [25]. Active colitis, autoimmunity or treated malignancy prior to HSCT did not confer inferior outcomes and should not prevent transplant referral. Patients who had undergone prior splenectomy had worse outcomes (both OS and EFS), which is likely multifactorial. In this patient group, splenectomy is used for severe, refractory autoimmunity or thrombocytopenia, or advanced liver disease, and thus may indicate advanced disease, and may increase risks of post-HSCT overwhelming sepsis [24,26]. As indications for splenectomy were not available, further interpretation is difficult.

For the entire cohort, OS and EFS are remarkable considering the degree of pre-HSCT morbidity. Survival was influenced by underlying IEI being significantly better for patients with phagocytic disorders (PD) and combined immune deficiencies (CID) compared to those with predominantly antibody deficiencies (PAD). The OS observed for patients with PD and CID is excellent, only exceeded by a few single-center studies with established experience in transplanting older IEI patients [11-13]. Our findings in the PAD group are consistent with previously reported inferior outcomes post-HSCT for CVID patients, although only 27 of the 39 patients in this group were characterized as classic CVID [10]. Notably, we did not observe the same high rates of GVHD in CVID patients described by Wehr *et al.* CVID patients referred for HSCT typically have complex CVID and associated inflammatory or autoimmune complications such as nodular regenerative hyperplasia (NRH) with hepatic impairment and/or GLILD [10,27,28]. Although our PAD subgroup was small, it is striking that younger patients with less pre-HSCT morbidity, particularly hepatic comorbidity, had a much better outcome, strongly supporting early consideration of HSCT, prior to the development of significant non-infectious complications. There remains an urgent need for additional

validated biomarkers to predict disease progression in CVID [29]. The overall very low rates of severe acute or chronic GVHD in this cohort are encouraging, especially for patients with non-malignant diseases. These may be explained by the high percentages (approximately 75% each) of transplants incorporating serotherapy, an HLA-matched donor, and reduced toxicity conditioning regimens.

The few available data in adults with IEI indicate worsening quality of life (QOL) with age, but comparable data on transplanted patients are absent [30,31]. QOL analysis pre- and post-HSCT should be addressed in prospective trials for older IEI patients. Nevertheless, >90% of survivors in our study had excellent performance scores and were attending school, university or work suggesting an acceptable QOL after successful HSCT, consistent with the limited published data [4,30,31].

Assessing the influence of conditioning regimens on outcome is difficult in a retrospective study as disease-specific considerations, patient age and comorbidity likely influence regimen selection. Accordingly, no impact of conditioning on outcome was seen in our study. Nevertheless, for patients with significant organ damage, regimens with reduced intensity and toxicity are likely to be preferred as supported by a recent prospective trial in a cohort of relatively old (50% >18 years) IEI patients with a median HCT-CI score of 3 [13]. The current IEWP guidelines for HSCT for IEI recommend three different reduced intensity regimens for adult patients [16]. Assessing longer term outcomes will be important to confirm the positive impact of HSCT on reducing recurrent events associated with underlying IEIs observed in untransplanted adults.

In conclusion, we report the largest cohort of older adolescents and adults with IEI having undergone HSCT, and have identified IEI subgroup, HCT-CI score and the cumulative number of IEI-related comorbidities as risk factors for adverse outcome. These data provide much needed evidence for physicians counseling IEI patients and their families, regarding the role of HSCT as a therapeutic intervention, and they should aid in designing appropriate prospective studies to define the preferred transplant approach for these patients. This data supports early referral of IEI patients regardless of their age, prior to the development of significant organ damage.

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AUTHOR CONTRIBUTIONS

ECM, MHA, ACL, NM, FS, MLF and ARG conceived and designed the study; TS managed the data; D-JE and KB performed the statistical analysis; MHA and ECM analyzed the data and wrote the manuscript; All authors except D-JE, TS and KB contributed clinical data; All authors reviewed and edited the manuscript. TS and D-JE directly accessed and verified the underlying data.

CONFLICTS OF INTEREST

MHA reports honoraria for educational events from Grifols and octapharma, support for attending meetings from octapharma, and stock ownership in and consulting fees from CSL Behring. CW reports participation on a Data Safety Monitoring Board or Advisory Board for Takeda. All other authors disclose no potential conflicts of interest.

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TABLES

		Total (N=329)	
		Missing (%)	**N (%)***
Patient sex	Male	0	223 (67.8%)
	Female	0	106 (32.2%)
IEI subgroup	CID	0	163 (49.5%)
	PD	0	127 (38.6%)
	PAD	0	39 (11.9%)
Age at HSCT (years)	Median (IQR)	0	18.4 (16.6-22.8)
Time from clinical diagnosis to HSCT (months)	Median (IQR)	1 (0.3%)	63.1 (13-189.1)
Age at clinical diagnosis (years)	Median (IQR)	3 (0.9%)	13 (3.6-17.2)
BMI at HSCT	Low BMI (<18)	34 (10.3%)	74 (25.1%)
	Normal/high BMI (≥18)		221 (74.9%)
Infection immediately prior to HSCT	No	45 (13.7%)	136 (47.9%)
	Yes		148 (52.1%)
Bronchiectasis at HSCT	Absent	5 (1.5%)	238 (73.5%)
	Present		86 (26.5%)
Colitis or protracted diarrhoea at HSCT	Absent	4 (1.2%)	255 (78.5%)
	Present		70 (21.5%)
Malignancy prior to HSCT^	No	5 (1.5%)	263 (80.9%)
	Yes		62 (19.1%)
Remission status at HSCT (if prior malignancy)	No remission	4 (5.6%)	23 (39.7%)
	Remission		33 (56.9%)
	Not evaluated		2 (3.4%)
GLILD at HSCT	No	18 (5.5%)	268 (86.2%)
	Yes		43 (13.8%)
Splenectomy prior to HSCT	No	14 (4.3%)	285 (90.5%)
	Yes		30 (9.5%)
Hepatic comorbidity	No	54 (16.4%)	239 (86.9%)
	Mild		22 (8%)
	Moderate/Severe		14 (5.1%)
IEI associated complications (bronchiectasis, colitis, malignancy, GLILD, hepatic comorbidity and splenectomy)	None	56 (17%)	90 (33%)
	One complication		99 (36.3%)
	Two or more complications		84 (30.8%)
HCT Comorbidity Index (Sorror Score)	HCT-CI 0	7 (2.1%)	89 (27.6%)
	HCT-CI 1-2		128 (39.8%)
	HCT-CI 3-4		59 (18.3%)
	HCT-CI > 4		46 (14.3%)

Table 1: Patient demographics

* Percentages in this column are calculated from the non-missing. ^All patients had established diagnosis of IEI prior to development of malignancy.

IEI: inborn error of immunity; IQR: interquartile ranges; CID Combined immunodeficiency; PD: Phagocyte disorders/innate; PAD: Predominantly antibody deficiency; HCST: hematopoietic stem cell transplant; BMI: body mass index; GLILD: granulomatous lymphocytic inflammatory lung disease

		CID		PAD		PD		
	Group							
		Median (IQR)		Median (IQR)		Median (IQR)		p
Age at HSCT	Median (IQR)	17.6 (16.4-21.2)		22.8 (17.4-37.9)		18.9 (16.8-22.5		***0.001***
		Missing	N (%)	Missing	N (%)	Missing	N (%)	p
Hepatic Comorbidity	No	28 (17.2%)	113 (83.7%)	3 (7.7%)	27 (75.0%)	23 (18.1%)	99 (95.2%)	***0.003***
	Mild		11 (8.1%)		7 (19.4%)		4 (3.8%)	
	Moderate/Severe		11 (8.1%)		2 (5.6%)		1 (1.0%)	
Splenectomy prior to HSCT	No	5 (3.1%)	133 (84.2%)	4 (10.3%)	31 (88.6%)	5 (3.9%)	121 (99.2%)	***<0.001***
	Yes		25 (15.8%)		4 (11.4%)		1 (0.8%)	
Bronchiectasis at HSCT	Absent	1 (0.6%)	119 (73.5%)	2 (5.1%)	21 (56.8%)	2 (1.6%)	98 (78.4%)	***0.032***
	Present		43 (26.5%)		16 (43.2%)		27 (21.6%)	
HCT-CI Score	HCT-CI 0	5 (3.1%)	51 (32.3%)	1 (2.6%)	9 (23.7%)	1 (0.8%)	29 (23.0%)	0.096
	HCT-CI 1-2		56 (35.4%)		12 (31.6%)		60 (47.6%)	
	HCT-CI >2		51 (32.3%)		17 (44.7%)		37 (29.4%)	

Table 2: Distribution of IEI-related comorbidities and age at HSCT by IEI subgroup.

		N (%)*
Donor type		
missing: 7 (2.1%)	MRD	103 (32%)
	MUD (10/10)	136 (42.2%)
	MMUD (9/10)	56 (17.4%)
	MMUD (<9/10)	8 (2.5%)
	UCB	1 (0.3%)
	MMRD (Haplo)	18 (5.8%)
Stem cell source		
missing: 1 (0.3%)	BM	151 (46%)
	PB	169 (51.5%)
	BM+PB	1 (0.3%)
	CB**	4 (1.2%)
	BM+CB	1 (0.3%)
	PB+CB	2 (0.6%)
Conditioning regimen intensity		
missing: 13 (4%)	myeloablative	82 (25.9%)
	reduced toxicity	208 (65.8%)
	non-myeloablative	26 (8.2%)
Serotherapy		
missing: 2 (0.6%)	Alemtuzumab	138 (42.2%)
	ATG/ALG	109 (33.3%)
	No serotherapy	80 (24.5%)
CMV match (donor/recipient)		
missing: 69 (21%)	-/-	74 (28.5%)
	-/+	18 (6.9%)
	+/-	60 (23.1%)
	+/+	108 (41.5%)
Year of HSCT		
	Median (IQR)	2014 (2010-2016)

		N (%)*
Graft manipulation		
missing: 1 (0.3%)	Yes	31 (9.5%)
	No	297 (90.5%)
	TCR alpha-beta depletion	16
	CD34 positive selection	10
	Other	5
Conditioning regimen groups		
missing: 2 (0.6%)	Busulfan-based	133 (40.4%)
	Treosulfan-based	86 (26.1%)
	Melphalan-based	74 (22.5%)
	Other	34 (10.4%)
Most commonly used conditioning regimens		
	Fludarabine Busulfan	97
	Fludarabine Melphalan	56
	Fludarabine Treosulfan	42
	Fludarabine Treosulfan Thiotepa	37
	Busulfan Cyclophosphamide	17
	Fludarabine Cyclophosphamide	13
	Fludarabine Melphalan Thiotepa	11
	Fludarabine Busulfan Thiotepa	7
	Fludarabine Melphalan BCNU	7
	Fludarabine Thiotepa	5
	Fludarabine	5
	Other	30

Table 3: Transplant characteristics.

*percentages in this column are calculated from the non-missing. ** one unrelated cord blood, all others from related donors.

MRD: matched related donor; MUD: matched unrelated donor; MMUD: mismatched unrelated donor; UCB: unrelated umbilical cord blood; MMRD: mismatched related donor; Haplo: haploidentical; BM bone marrow; PB peripheral blood; CB cord blood; ATG/ALG anti-thymocyte globulin/anti-lymphocyte globulin; MAbs monoclonal antibodies; TCR T-cell receptor.

Group	N	Overall Survival			N	Event Free Survival		
		6 months (95% CI)	1 year (95% CI)	5 years (95% CI)		6 months (95% CI)	1 year (95% CI)	5 years (95% CI)
Whole Cohort	329	83% (79-87)	78% (74-83)	71% (66-76)	319	70% (65-75)	65% (60-71)	62% (56-67)
CID	163	80% (74-86)	76% (69-83)	68% (61-76)	157	68% (61-75)	64% (56-71)	58% (50-67)
PD[$]	127	93% (88-97)	87% (81-93)	78% (71-86)	123	77% (70-85)	72% (64-80)	69% (61-77)
CGD alone^	*83*	*92% (86-98%)*	*83% (75-91%)*	*77% (67-86%)*	*80*	*74% (64-83%)*	*69% (59-79%)*	*67% (57-78%)*
PAD[$$]	39	64% (49-79)	59% (44-74)	59% (44-74)	39	54% (38-69)	51% (36-67)	51% (36-67)
CVID alone^^	*27*	*56% (37-74)*	*48% (29-67)*	*48% (29-67)*	*27*	*44% (26-63)*	*41% (22-59)*	*41% (22-59)*

Table 4: Estimated OS and EFS for whole cohort and IEI subgroups.

^subset of PD; ^^subset of PAD.

[$] PD including CGD; [$$] PAD including CVID

Risk factor	Group	N at risk	N events	HR (95% CI)	P value	LRT*
IEI Subgroup	CID	127	39			0.052
	PAD	30	15	1.49 (0.78-2.86)	0.2	
	PD	102	21	0.62 (0.36-1.07)	0.09	
IEI complications	No complication	88	18			0.062
	1 complication	91	24	1.02 (0.54-1.94)	0.9	
	≥2 complications	80	33	1.84 (0.98-3.48)	0.06	
Age at HSCT	(decades)	259	75	1.13 (0.87-1.46)	0.4	0.378
HCT-CI Score	HCT-CI 0	68	17			0.103
	HCT-CI 1-2	105	23	0.87 (0.45-1.67)	0.7	
	HCT-CI >2	86	35	1.54 (0.82-2.9)	0.18	
Conditioning intensity	MA	69	26			0.32
	RTC	169	44	0.69 (0.42-1.13)	0.14	
	NMA	21	5	0.66 (0.25-1.76)	0.4	

5A: Multivariable analysis of risk factors for OS.

Risk factor	Group	N at risk	N events	HR (95% CI)	P value	LRT*
IEI Subgroup	CID	122	50			0.142
	PAD	30	17	1.38 (0.76-2.48)	0.3	
	PD	101	33	0.73 (0.47-1.16)	0.18	
IEI complications	No complication	86	27			***0.05***
	1 complication	88	32	1.06 (0.62-1.8)	0.8	
	≥2 complications	79	41	1.78 (1.04-3.04)	*0.035*	
Age at HSCT	(decades)	253	100	1.15 (0.92-1.44)	0.2	0.249
HCT-CI Score	HCT-CI 0	64	23			0.774
	HCT-CI 1-2	104	38	0.92 (0.53-1.59)	0.8	
	HCT-CI >2	85	39	1.09 (0.62-1.91)	0.8	
Conditioning intensity	MA	68	27			0.958
	RTC	164	65	1.05 (0.66-1.66)	0.8	
	NMA	21	8	0.96 (0.43-2.15)	0.9	

5B: Multivariable analysis of risk factors for EFS.

* p value for: does this risk factor add information when the other risk factors are already in the model? (<0.05 = yes). LRT: Likelihood ratio test.

Table 5: Multivariable analyses of risk factors for OS and EFS.

		At last assessment				
		<2 years post HSCT*		**≥2 years post HSCT****		
Time to last assessment	median (IQR)	4.8 months (2.4-12.3)		60.9 months (42-91.5)		
		missing (%)	**n (%)***	**missing (%)**	**n (%)***	
Total			104 (100%)		225 (100%)	
IgRT	no	44 (42.3%)	23 (38.3%)	9 (4%)	185 (85.6%)	
	yes		22 (36.7%)		25 (11.6%)	
	not evaluated		8 (13.3%)		2 (0.9%)	
	unknown		7 (11.7%)		4 (1.9%)	
			median (IQR)		median (IQR)	normal range**
Lymphocytes (10^9/L)		66 (63.5%)	1.1 (0.6-2.2)	50 (22.2%)	2.0 (1.3-3.2)	1.00-4.80
CD3+ T-cells (10^9/L)		79 (76%)	0.8 (0.3-1.6)	107 (47.6%)	1.2 (0.7-2.0)	0.79-2.01
CD4+ T-cells (10^9/L)		81 (77.9%)	0.2 (0.1-0.5)	104 (46.2%)	0.6 (0.4-1.2)	0.45-1.25
CD8+ T-cells (10^9/L)		81 (77.9%)	0.5 (0.2-0.6)	104 (46.2%)	0.6 (0.3-1.5)	0.22-0.69
CD56+ NK-cells (10^9/L)		81 (77.9%)	0.2 (0.1-0.3)	113 (50.2%)	0.2 (0.1-3.1)	0.10-0.44
CD19+ B-cells (10^9/L)		81 (77.9%)	0 (0-0.3)	118 (52.4%)	0.4 (0.2-1.1)	0.11-0.36
Naïve T-cells (10^9/L)		96 (92.3%)	0 (0-0.1)	177 (78.7%)	0.5 (0.2-1.5)	0.19-0.98

Table 6: Immune reconstitution.

* last assessment is before 2 years post HSCT for 104 patients who were lost to FU or died before 2 years.

** only patients alive and in follow-up by 2 years post HSCT; IgRT Immunoglobulin replacement therapy.

*** percentages in this column are calculated from the non-missing.

FIGURE LEGENDS

Figure 1. Kaplan-Meier estimated probabilities of overall survival (OS) at 5 years.
(A) The estimated OS for the whole cohort was 78% (95% CI: 74-83%) at 1 year and 71% (66-76%) at 5 years post-HSCT. OS at both 1 year and 5 years post-HSCT were influenced by: (B) IEI subgroup; (C) the presence of bronchiectasis at HSCT (D) splenectomy prior to HSCT; (E) hepatic comorbidity at HSCT; (F) the number of IEI associated risk factors at HSCT (bronchiectasis, colitis, malignancy, GLILD, hepatic comorbidity and splenectomy); (G) HCT-CI score; and (H) year of transplant. OS at both 1 and 5 years post-HSCT were *not* influenced by: (I) Age at HSCT.
Estimated OS at 5 years (95% CI) are shown.

Figure 2. Kaplan-Meier estimated probabilities of event free survival (EFS) at 5 years.
(A) The estimated EFS for the entire cohort was 65% (95% CI: 60-71%) at 1 year and 62% (56-57%) at 5 years post-HSCT. EFS at both 1 year and 5 years post-HSCT were influenced by: (B) IEI subgroup; (C) the presence of bronchiectasis at HSCT; (D) splenectomy prior to HSCT; and (E) the presence of hepatic dysfunction at HSCT. EFS at both 1 year and 5 years post-HSCT were *not* influenced by: (F) number of IEI associated risk factors (bronchiectasis, colitis, malignancy, GLILD, hepatic comorbidity and splenectomy); (G) HCT-CI score; (H) year of transplant; or (I) age at HSCT.
Estimated EFS at 5 years (95% CI) are shown.

Figure 3. Cumulative incidence of acute and chronic graft versus host disease.
The cumulative incidence of (A) grades II-IV acute GVHD was 22% (17-26%) at both 6 and 12 months post-HSCT (black line), with 8% (5-11%) developing grades III-IV aGVHD at both 6 and 12 months post-HSCT (red line).
The cumulative incidence of (B) all chronic GVHD (limited and extensive) was 16% (12-20%) at 1 year and 19% (15-24%) at 5 years (black line), whilst extensive chronic GVHD was seen in 7% (4-9%) at 1 year and 7% (4-10%) at 5 years (red line).

Figure 4. Whole blood, T cell and myeloid chimerism at last follow-up.
Degree of donor chimerism at last follow-up in patients with available data (numbers indicated for each category). Left column: whole blood, middle column: T-cell, right column: myeloid chimerism.