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Allogeneic stem cell transplantation compared to conservative management in adults with inborn errors of immunity and life-threatening complications: an international retrospective matched pairs analysis.

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

3

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70 cell transplantation; matched pairs analysis; mean cumulative number of recurrent
71 events analysis.

72

73 **Keypoints:**

74 1. Non-transplanted adults with CGD and CID have an ongoing risk of severe
75 events compared to transplanted patients.

76 2. AlloSCT prevents progressive morbidity associated with IEI in adults, which
77 may outweigh the negative impact of TRM.

78 **ABSTRACT**

79

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

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

92 281 patients were included (79 transplanted, 202 non-transplanted). Median age at
93 transplant was 21 years. Transplant indications were mainly lymphoproliferative
94 disease ($n=23$) or colitis ($n=15$). Median follow-up was 4.8 years (IQR [2.5-7.2]).
95 One-year TRM was 13%. Estimated DFS at 5 years was higher in transplanted
96 patients (58% vs. 33%, $p=0.007$). Non-transplanted patients had an ongoing risk of
97 severe events with an increased mean cumulative number of recurrent events
98 compared to transplanted patients. Sensitivity analyses removing patients with CVID
99 and their matched transplanted patients confirm these results. AlloSCT prevents
100 progressive morbidity associated with IEI in adults, which may outweigh the negative
101 impact of TRM.

102

103 **INTRODUCTION**

104

105 Inborn errors of immunity (IEI) are a heterogeneous group of diseases leading to a
106 predisposition to infections, autoimmune or autoinflammatory manifestations,
107 lymphoproliferation and malignancies. In less severe IEI near-normal life expectancy
108 can be achieved with supportive care. However, in many IEI, life-threatening
109 complications severely compromise quality of life and result in premature mortality.
110 Allogeneic stem cell transplantation (alloSCT) is the standard of care for patients with
111 severe combined immune deficiency and is commonly performed for children with
112 various life-threatening IEI¹⁻⁶. In older patients, transplant outcomes were historically
113 poor and despite improved results with reduced-intensity conditioning (RIC),
114 indications for and timing of transplant remain controversial in older patients⁷. The
115 role of non-alloSCT therapies such as targeted agents and the so far exceptional gene
116 therapy techniques in treatment algorithms for older patients are still mostly
117 undefined⁸⁻¹¹.

118

119 Risks of alloSCT in older patients are outweighed by the potential benefits in IEI with
120 predictably severe clinical phenotype, such as primary HLH or inherited bone marrow
121 failure. However, decisions around transplantation in IEI with a variable clinical
122 phenotype or sparse long-term outcome data are more challenging¹¹⁻¹⁹. This includes
123 patients with immunodeficiency affecting cellular and humoral immunity termed
124 combined immunodeficiencies (CID), including immune dysregulation syndrome
125 (IDS), late onset CID (LoCID) and common variable immune deficiency with serious
126 non-infectious complications ('complex-CVID'), as well as patients with chronic

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

129

130 In adults with severe IEI, comorbidities and organ dysfunction are frequent leading to
131 higher transplant-related mortality (TRM) rates²⁰⁻²². In order to reduce the TRM, RIC
132 regimens have been used. A large prospective study demonstrated that RIC-alloSCT
133 was safe and effective in patients with CGD, including 25 (45%) adolescent and
134 young adults (14-39 years)²³. In addition, more recent data has demonstrated that RIC
135 approaches in carefully selected patients result in excellent overall survival (OS) in
136 young adult patients^{11,24}. We have recently reported similarly excellent outcomes after
137 reduced-intensity conditioned alloSCT in adult IEI patients (85.2% 3-year OS)²⁵.
138 Very recently, a large retrospective study of alloSCT in CGD reported excellent
139 outcomes with a 76% 3-year OS for patients ≥ 18 years, independent of conditioning
140 regimen used²², in line with a recent EBMT retrospective study demonstrating no
141 impact of conditioning intensity on OS in a wider group of IEI transplanted ≥ 15
142 years²⁶.

143

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

148

149 **PATIENTS AND METHODS**

150

151 *Patients*

152 The study population included all IEI patients recorded in the French National
153 Reference Center for IEI (CEREDIH) or the Royal Free London Hospitals (RFH)
154 registries. All living patients gave their written informed consent (**Supplementary**
155 **data**). Transplanted patients were included if they fulfilled the following criteria: (a)
156 age at first alloSCT ≥ 15 years; (b) transplanted between January 2008 and December
157 2018; (c) IEI diagnosis of CGD or CID. The CID group included patients diagnosed
158 with an IDS, LoCID or CVID according to the diagnostic framework of the referring
159 physician (**Supplementary Table 1**). Twenty-two patients have been previously
160 reported²⁵. Data were collected retrospectively from the medical notes and registries.
161 The dataset was censored in November 2019.

162

163 *AlloSCT procedure*

164 Conditioning regimens were classified as full-intensity conditioning or reduced
165 intensity conditioning regimens (including intravenous busulfan ≤ 9.6 mg/kg total
166 dose) as previously described²⁷. For CGD patients, the recommended conditioning
167 regimen is based on a large study showing the safety of a RIC regimen consisting of
168 high-dose fludarabine, serotherapy and low-dose or targeted busulfan
169 administration²³. For CID patients, the clinical practice is more heterogenous and
170 depends on the patient's comorbidities, the characteristics of the underlined IEI and
171 the usual practice in the center. The recently published updated EBMT/ESID inborn
172 errors working party guidelines for alloSCT for IEI include a chapter on
173 recommendations for the management of adolescent and adult patients together with

174 guidance on disease-specific conditioning regimens²⁸. Patients and donors were
175 matched for HLA-A, -B, -C, -DRB1, and -DQB1 by intermediate or high-resolution
176 DNA typing as appropriate. Peripheral blood chimerism was defined as “mixed” if
177 donor DNA was $\leq 95\%$. The pretransplant hematopoietic cell transplantation-specific
178 comorbidity index (HCT-CI) scores pretransplant were calculated for all patients^{29,30}.

179

180 *Matching procedure*

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

196

197 *Statistics*

198 Categorical and continuous variables were compared by either χ^2 or Fisher exact tests
199 where relevant and by Mann-Whitney test, respectively. The baseline of all survival
200 analyses was the age at alloSCT (randomization age for the controls). OS was defined
201 as the time between baseline until death from any cause, and disease-free survival
202 (DFS) as time between baseline and IEI-related events (defined by infection requiring
203 hospitalization, severe autoimmune or inflammatory manifestation requiring systemic
204 immunosuppression, malignancy) or death, whichever occurred first. Patients with no
205 event were censored at the time of their last follow-up. The probability of dying from
206 transplant-related complications (TRM) was estimated. To further analyze outcomes
207 for patients who survived the first year following transplant, conditional overall
208 survival (COS) was defined as the probability of surviving an additional number of
209 years given that the patient has already survived one year. OS, COS and DFS curves
210 were estimated using the Kaplan-Meier estimator and comparisons between alloSCT
211 and non-transplanted patients were performed using the log-rank test. We then
212 estimated the mean cumulative number of recurrent events (REs) using the Ghosh's
213 estimator³¹, which accommodates for the competing risk of death. REs were
214 categorized as IEI and/or alloSCT-related events (defined as infection requiring
215 hospitalization, severe autoimmune or inflammatory manifestations, malignancy,
216 grade 3-4 acute and extensive chronic GVHD, graft failure, CD34⁺ cell top up, donor
217 lymphocyte infusion (DLI), post-transplant lymphoproliferative disease, viral
218 reactivation requiring systemic anti-viral or cellular therapies). We emphasize that
219 accounting for competing risks is critically important for this study as deceased
220 patients can no longer be considered at risk for experiencing REs. Without
221 incorporating competing risks into the analysis, an overestimation of the mean
222 cumulative number of REs would occur. Cox regression models were implemented

223 for death (from all causes) and for REs. The Cox model for death was clustered on
224 match criteria and included the identified risk factors (sex, birth decade, IEI category
225 (CGD or CID), genetic diagnosis, lymphoproliferative disease, autoimmunity,
226 aspergillosis, solid cancer, age more or less than 25 years old at alloSCT) as well as
227 treatment group (alloSCT vs. non-alloSCT) with backward selection (selection criteria
228 was $\alpha = 0.2$, lymphoproliferative disease, autoimmunity, aspergillosis, alloSCT vs.
229 non-alloSCT). Moreover, considering that complications have a limited impact on
230 survival after five years, complications were coded in the Cox model as binary time-
231 dependent covariates which indicate at any time point if patients had the complication
232 in the last five years or not. The Cox model for REs was implemented with the same
233 set of covariates and robust sandwich standard error estimates were used to adjust for
234 multiple events for the same patient³². In both Cox models, time dependent covariates
235 were taken into account using the counting process approach³³ ([https://cran.r-
236 project.org/web/packages/survival/vignettes/timedep.pdf](https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf)) (**Supplementary Figure**
237 **1**). All analyses were performed using R software version 3.6.1 (R Core Team 2018).
238

239 **RESULTS**

240

241 *Patients' characteristics at baseline*

242 In total, 281 patients were included, comprising 79 transplanted and 202 non-
243 transplanted patients. Twenty CGD and 59 CID patients received a first alloSCT
244 between 2008 and 2018 in London or in France (**Figure 1**). According to matching
245 criteria, patients were equally distributed with respect to age at last review (median
246 age 25y, IQR [20–30] vs. 26y, IQR [21–33] in non-transplanted patients, $p = 0.152$),
247 IEI category (CGD or CID), and lymphoproliferative disease (28% vs. 24% in non-
248 transplanted patients, $p = 0.533$). The distribution of IEI diagnoses was different in
249 CID patients ($p < 0.001$), with less CVID diagnoses (1% vs. 31% in non-transplanted
250 patients) and more profound T-cell deficiencies (73% vs. 45% in non-transplanted
251 patients) (**Supplementary Table 3**). However, non-transplanted patients identified as
252 CVID by their referring physician were similar to those identified as LoCID/IDS in
253 terms of IEI-related complications (**Supplementary Table 4**). Moreover, a profound
254 T-cell deficiency (identified by $CD4 < 200/mm^3$ or naive T-cell deficiency) was
255 identified in 19% of CVID patients. In contrast 30% of CID/IDS patients did not have
256 a quantitative T-cell deficiency (**Supplementary Table 5**). Transplanted CID patients
257 had higher comorbidity scores, with an increased incidence of prior or active
258 infections compared to the non-transplanted CID control group ($p < 0.001$). Non-
259 transplanted CID patients had more frequent interstitial pulmonary involvement (3%
260 in transplanted vs. 15% in non-transplanted patients, $p = 0.017$). Of the 23 non-
261 transplanted patients with lung involvement, 9 had CTLA-4/LRBA deficiency (**Table**
262 **1**). Patients with CGD had similar comorbidities between the two groups (**Table 2**).

263

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

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

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

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

299

300 *Allogeneic stem cell transplantation procedures*

301 Fourteen females (18%) and 65 males (82%) received an alloSCT at a median age of
302 21 years (IQR [17–28], **supplementary Figure 2A**). The median time from age at
303 clinical diagnosis of IEI to alloSCT was 13.3 years (IQR [5.0-19.2]). Most of the
304 patients were transplanted after 2015 (n=47/79, **supplementary Figure 2B**). Forty-
305 six patients received RIC (58%) and 33 myeloablative conditioning regimens (42%)²⁷.
306 Conditioning for CGD patients consisted of fludarabine, busulfan with alemtuzumab
307 for 9 patients or rabbit ATG for 11 patients. Patients with CID mainly received
308 fludarabine combined with melphalan 140 mg/m², busulfan, or treosulfan. Patients
309 transplanted with an haploidentical donor received a Baltimore regimen using high-
310 dose posttransplant cyclophosphamide³⁴. Details are shown in **Table 4**. Thirty
311 patients had matched related donors (MRD; siblings), 33 matched unrelated donors
312 (MUD; 10/10 antigen matched unrelated donor), twelve mismatched unrelated donors
313 (MMUD; with 1 antigen mismatched unrelated donor) and four haploidentical donors.

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

320

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

334

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

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

346

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

359

360 *Outcome of transplanted versus matched non-transplanted patients*

361 With a median follow-up of 4.8 years (IQR [2.5-7.2]), the projected 5-year DFS was
362 58% (95% CI, 46% to 75%) in the alloSCT group versus 33% (95% CI, 27% to 42%)
363 in non-transplanted patients ($p = 0.007$) (**Figure 3A**). The estimated one-year TRM

364 was 13% (95% CI, 5% to 20%, **Figure 3B**). Projected 5-year cumulative incidence of
365 mortality was higher in the alloSCT group (30%; 95% CI, 14% to 42% vs. 11%; 95%
366 CI, 6% to 15% in non-transplanted patients; $p < 0.001$; **Figure 3D**). Since the effect
367 of alloSCT on survival is time-dependent, we considered two periods for the
368 multivariate analysis: the first period covering the first year after the procedure and
369 the late period after the first year. The 5-year conditional OS (COS) was similar for 1-
370 year survivors between both cohorts (84%; 95%CI, 71% to 100% vs. 90%; 95%CI,
371 86% to 95% in non-transplanted patients; **supplementary Figure 3**). Multivariable
372 analysis revealed that alloSCT during the first period, invasive aspergillosis,
373 autoimmunity and lymphoid malignancy were significantly associated with death
374 (hazard ratio for alloSCT-first year, 5.43; 95% CI, 1.84 to 16.02; $p < 0.01$).
375 Conversely, after the first year following the procedure, alloSCT was no longer
376 associated with death (hazard ratio for alloSCT-late period, 1.49; 95% CI, 0.51 to
377 4.31; $p = 0.46$) (**Figure 4**). Therefore, the excess risk of alloSCT on OS was only
378 significant during the first year post transplant.

379

380 In order to estimate the quality of life of non-transplanted versus transplanted IEI
381 patients, we assessed the mean cumulative number of recurrent events (REs),
382 examining first and subsequent events simultaneously, including both IEI-related and
383 transplant-related morbidities. At one year, the mean cumulative number of REs was
384 0.42 in the alloSCT group versus 0.12 in non-transplanted patients. After four years,
385 the number of REs was reversed between the two groups (for example, REs at eight
386 years were 0.59 in transplanted patients compared to 1.08 in non-transplanted
387 patients). Overall, beyond one-year post alloSCT, transplanted patients developed
388 very few complications resulting in a plateau, while non-transplanted patients had a

389 continuously increased and progressive risk for severe IEI-related complications
390 (**Figure 3C**). Multivariate analysis revealed that alloSCT during the first period,
391 autoimmunity and lymphoid malignancy were significantly associated with recurrent
392 events (hazard ratio for alloSCT-first year, 3.79; 95% CI, 2.29 to 6.26; $p < 0.01$).
393 However, transplanted patients had significantly less recurrent events after the first
394 year following the alloSCT procedure (hazard ratio for alloSCT-after first-year, 0.25;
395 95% CI, 0.1 to 0.6; $p < 0.01$) (**Figure 4**). Separate analyses for the CGD and CID
396 groups are shown in **supplementary Figures 4 and 5**. As the number of patients
397 labelled with a diagnosis of CVID, a complex, heterogeneous and incompletely
398 understood disease entity, is much higher in the non-transplanted group, which may
399 indicate that both intrinsic disease characteristics as well as disease manifestations
400 were not properly matched between the alloSCT and non-alloSCT group, we
401 performed sensitivity analysis by removing patients identified as CVID without
402 breaking the matching. After their removal, 139 non-transplanted patients were
403 compared to 72 transplanted patients with similar results in terms of OS, DFS and
404 mean cumulative number of REs (**Supplementary Figure 6**), suggesting that patients
405 with severe CVID had similar prognosis to patients with severe CID/IDS. These
406 results were also similar in the subgroup of patients with CID (w/o CGD patients) and
407 in sensitivity analysis by removing patients with CVID and/or lung involvement (data
408 not shown).
409

410 **DISCUSSION**

411

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

418

419 There is ongoing debate about the role of alloSCT in older adolescents and adults
420 with IEI, including specific indications for transplant and optimal timing. As
421 prospective studies in such rare, heterogeneous diseases are difficult, we conducted a
422 retrospective case-control study to explore the role of alloSCT. As expected,
423 transplanted patients had severe IEI phenotypes; most had active complications at the
424 time of alloSCT, high HCT-CI scores and at least an HCT-CI score of one in 86% of
425 patients. As previously published, the most common indications for alloSCT were
426 severe active colitis or invasive aspergillosis in CGD patients^{22,23} and malignant
427 lymphoproliferative disease³⁵, infection or complex immune dysregulation in CID
428 patients^{20,25}. Transplant-related mortality was 15% in CGD patients (3/20), which is
429 consistent with previous reports²³ and a recently reported 2-year OS of 78% in a large
430 retrospective EBMT study including 77 adult CGD patients²². In the CID patient
431 group, the TRM was 19% (11/59). A retrospective study of patients with complex
432 CVID who underwent alloSCT, reported higher mortality rates in 14 patients aged
433 18–50 years who had an OS of 57%, 21% graft failure and 21% severe GVHD²⁰. On
434 the contrary, excellent outcome has been recently reported in six CGD and 12 other

435 IEI patients aged 15 to 22 years, with an OS of 94%¹¹, in line with our previous study
436 of RIC alloSCT in adult IEI patients reporting a 3-year OS of 85%²⁵. A prospective
437 clinical trial of a novel radiation free and serotherapy-free RIC, T-replete transplant
438 platform in patients with IEI (including CID patients with various genetic diagnoses)
439 showed encouraging preliminary results for the first 20 patients (including 10 aged
440 over 18) with an 1-year OS at 90% and low incidence of GVHD (NCT02579967)²⁴.
441 The majority of recent data in adults with IEI has shown RIC alloSCT to be safe and
442 effective, even in patients with high-risk pretransplant morbidity scores^{11,20,22,24,25}. In
443 contrast, a recent EBMT retrospective study analyzing outcome post alloSCT for
444 adult IEI patients demonstrated no impact of conditioning intensity on OS or event-
445 free survival²⁶. In our study and as with other published studies, mortality was higher
446 in patients aged at alloSCT of more than 25 years old and in those with higher
447 comorbidity scores, suggesting that alloSCT should be undertaken earlier in the
448 medical history of a patient with a severe IEI. Finally, alloSCT survivors experienced
449 a continuous improvement with evidence of phenotype reversal over time, including
450 those with mixed chimerism at last review.

451

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

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

466

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

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

494

495 The results of our study highlight the need for consensus recommendations on the
496 timing of and indication for alloSCT in adult patients with severe IEI⁷ and indeed, the
497 most recent international published guidelines on alloSCT include a section on adult
498 IEI patients²⁸. In patients with CGD, complications increase as patients age justifying
499 the discussion of alloSCT whenever a patient has a suitable donor. In patients with
500 severe CID, the decision is more complex and is influenced by the type of CID,
501 disease severity, comorbidities, and donor availability. Typically, there are 2 main
502 categories of patients: (1) where the indication for alloSCT is clear (e.g. well-
503 characterized gene defect with predictable poor prognosis and severe previous IEI-
504 related complications) and the patients has an HCT-CI score between 0 and 2 and an
505 appropriately matched donor; (2) where alloSCT is predicted to result in excessively
506 high TRM (patients with an HCT-CI score of at least 3 and multiple IEI-associated
507 complications at transplant) or is impossible due to the absence of a suitable donor²⁶.
508 In these patients, the individual benefit-risk balance should be carefully discussed
509 with the patient and at a specialist multidisciplinary team (MDT) meeting. Proceeding

510 to alloSCT may be indicated depending on the severity of the underlying IEI. In all
511 cases, recommendations need to be balanced by the availability of and response to
512 potentially effective targeted therapies (such as abatacept in LRBA/CTLA-4
513 deficiency). Patients should be discussed at a specialist MDT meeting, with clinicians
514 experienced in alloSCT for adult IEI patients. Work is in progress to validate the
515 immune deficiency and immune dysregulation activity (IDDA) score³⁶ in predicting
516 outcome following alloSCT in adults with IEI.

517

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

525

526

527

528 **Authorship contributions:** MC, ECM, FS, NM, SB and TAF conceptualized,
529 supervised the study and wrote the manuscript. MC, TAF provided data and data
530 analysis. MA, OB, MC, NM, FS and JPJ performed statistical analysis. All authors,
531 except MA and OB provided clinical care for the patients described. MC obtained
532 fundings. All authors edited and approved the final version of the paper. MC, ECM,
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534

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665

666

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679

680 **FIGURE LEGENDS**

681

682 **Figure 1: Flow-chart**

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

693

694 **Figure 2: Evolution of disease following alloSCT**

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

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

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

707

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

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

723

724 **Figure 4: Cox multivariate analysis**

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

728

729 TABLES

730

731 Table 1: Comparisons of IEI-related complications in transplanted and matched

732 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				
<i>Bacterial infection</i>	101 (48%)	60 (39%)	41 (69%)	<0.001
<i>Viral infection*</i>	32 (15%)	7 (5%)	25 (42%)	<0.001
<i>Parasitic infection</i>	8 (4%)	2 (1%)	6 (10%)	0.007
<i>Invasive aspergillosis</i>	11 (5%)	5 (3%)	6 (10%)	0.042
Autoimmune cytopenia				
<i>Autoimmune neutropenia</i>	27 (14%)	19 (12%)	8 (18%)	0.327
<i>Autoimmune hemolytic anemia</i>	47 (23%)	42 (27%)	5 (10%)	0.011
<i>Autoimmune thrombocytopenia</i>	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				
<i>Lymphoid proliferation</i>	70 (33%)	48 (31%)	22 (37%)	0.412
<i>Myeloid malignancy</i>	2 (1%)	1 (1%)	1 (2%)	0.48
<i>Solid cancer</i>	11 (5%)	8 (5%)	3 (5%)	1

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

738

739 Table 2: Comparisons of IEI-related complications in transplanted and matched

740 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				
<i>Bacterial infection</i>	56 (81%)	37 (76%)	19 (95%)	0.09
<i>Viral infection</i>	1 (1%)	1 (2%)	0 (0%)	1
<i>Fungal infection</i>	33 (48%)	22 (45%)	11 (55%)	0.446
<i>Invasive aspergillosis</i>	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%)	<i>1</i>
Lymphoid proliferation	1 (1%)	1 (2%)	0 (0%)	<i>1</i>

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

743

744 **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	<i>1</i>	<i>0</i>	<i>1</i>

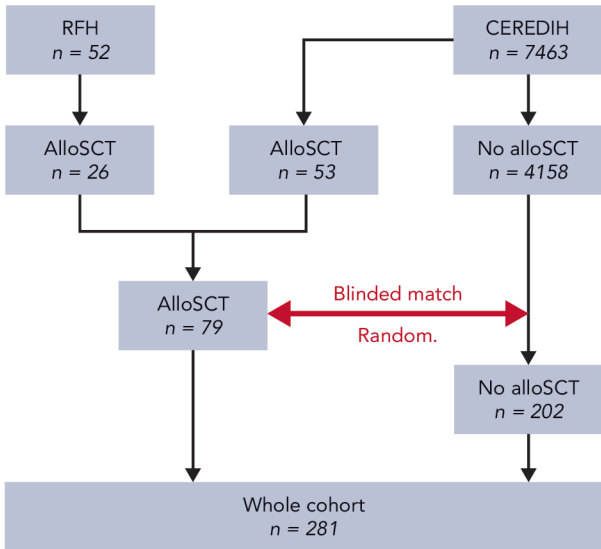
745 *Malignant lymphoproliferative disease (except one patient with Bowen disease); **Crohn-like colitis
746 (except one patient with Cryptosporidium associated-enteropathy); ***Nodular regenerative
747 hyperplasia, sclerosing cholangitis, one patient had hepatitis T-cell infiltration and another had EBV-
748 associated hepatitis; AI: autoimmune; NA: non available.
749

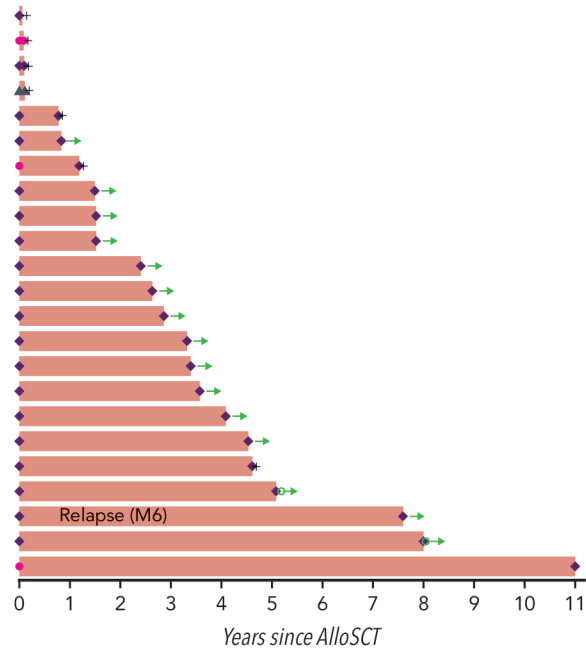
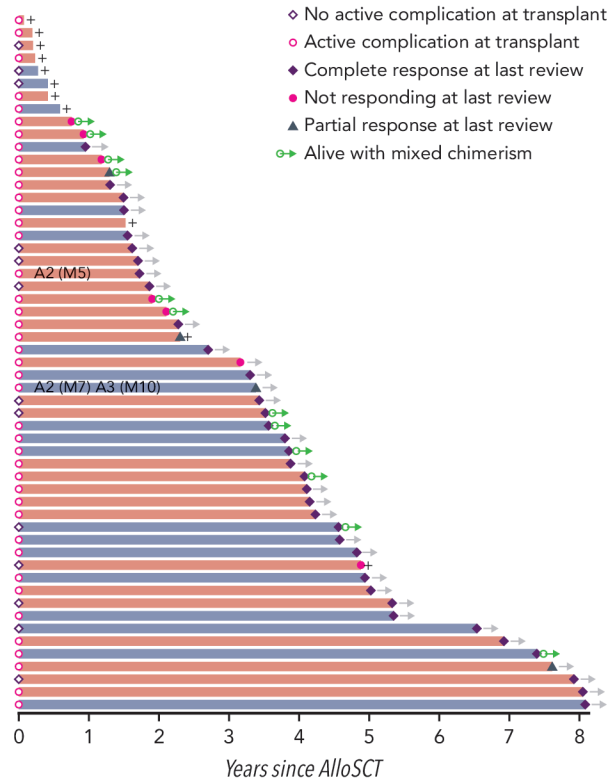
750 **Table 4: Characteristics of allogeneic stem cell transplantation procedure.**

	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	<i>1</i>	<i>0</i>	<i>1</i>
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%)

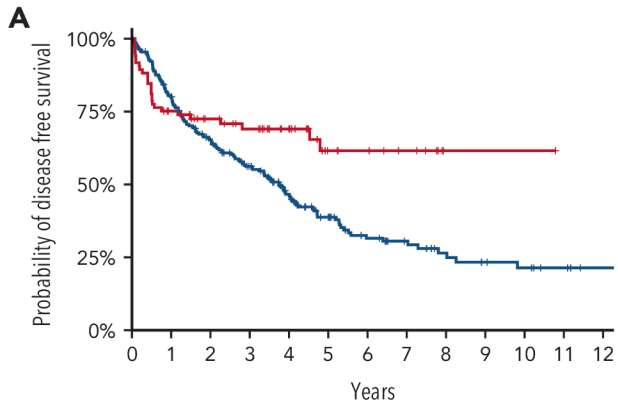
	Flu/Bu/Thiotepa	2 (3%)	0 (0%)	2 (3%)
	CCP/Bu	1 (1%)	0 (0%)	1 (2%)
	CCP/TBI (12Gy)	2 (3%)	0 (0%)	2 (3%)
	CCP/Flu	1 (1%)	0 (0%)	1 (2%)
	Flu/TBI (2Gy)	1 (1%)	0 (0%)	1 (2%)
<i>In-vivo</i> T-cell depletion	Alemtuzumab	36 (46%)	9 (45%)	27 (46%)
	ATG	29 (37%)	11 (55%)	18 (31%)
GVHD prophylaxis	Cyclosporine	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%)

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

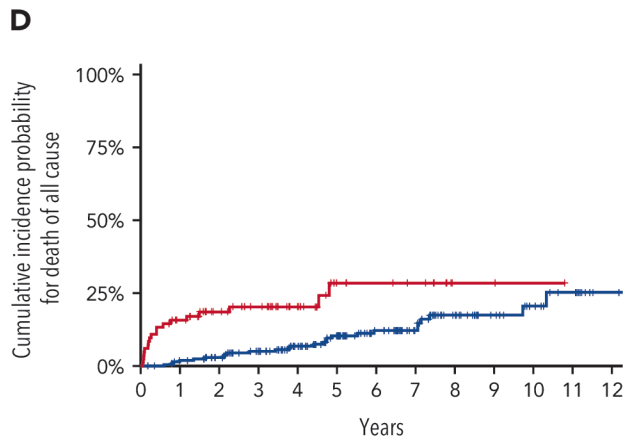
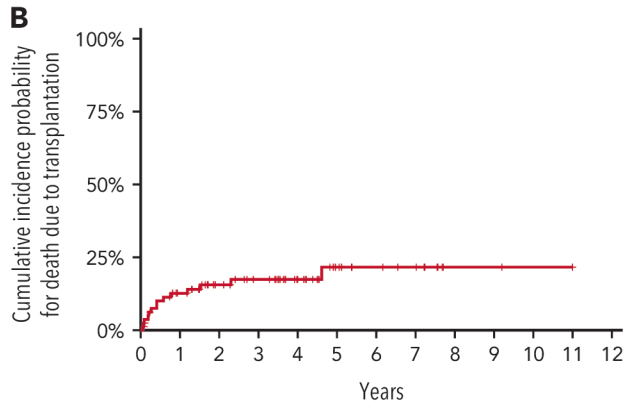


A Patients transplanted for lymphoproliferative disease**B** Patients transplanted for other IEI-related complications

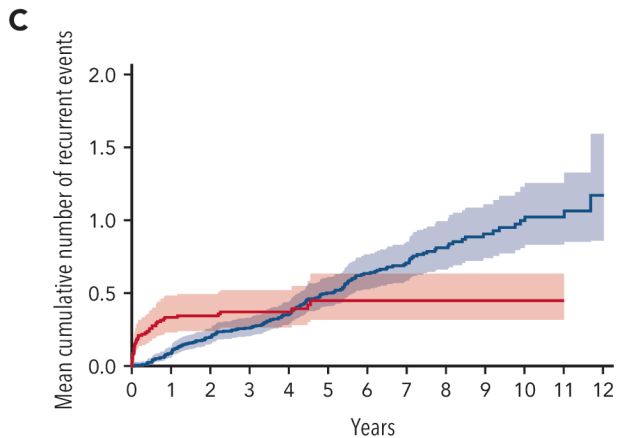
- ◇ No active complication at transplant
- Active complication at transplant
- ◇ Complete response at last review
- Not responding at last review
- ▲ Partial response at last review
- ➔ Alive with mixed chimerism



No alloSCT	201	156	118	93	64	42	26	19	12	10	8	4	1
AlloSCT	78	54	40	34	25	13	9	7	3	1	1	0	0



No alloSCT	201	194	179	164	141	116	89	67	43	29	23	13	4
AlloSCT	79	62	46	39	27	15	11	9	4	2	1	0	0



Hazard-ratio for death

Hazard-ratio for recurrent events

