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Received: 11 October 2023 | Revised: 23 February 2024 | Accepted: 4 March 2024

DOI: 10.1002/ajh.27293

RESEARCH ARTICLE

AJH WILEY

HLA-haploidentical stem cell transplantation in children with inherited bone marrow failure syndromes: A retrospective analysis on behalf of EBMT severe aplastic Anemia and pediatric diseases working parties

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Abstract

Haploidentical stem cell transplantation (haplo-SCT) represents the main alternative for children with inherited bone marrow failure syndrome (I-BMF) lacking a matched donor. This retrospective study, conducted on behalf of the EBMT SAAWP and PDWP, aims to report the current outcomes of haplo-SCT in I-BMFs, comparing the different in vivo and ex vivo T-cell depletion approaches. One hundred and sixty-two I-BMF patients who underwent haplo-SCT (median age 7.4 years) have been registered. Fanconi Anemia was the most represented diagnosis (70.1%). Based on different T-cell depletion (TCD) approaches, four categories were identified: (1) TCR$\alpha\beta^+$/CD19$^+$-depletion (43.8%); (2) T-repleted with post-transplant Cyclophosphamide (PTCy, 34.0%); (3) In-vivo T-depletion with ATG/alemtuzumab (14.8%); (4) CD34$^+$ positive selection (7.4%). The cumulative incidences (CI) of neutrophil and platelet engraftment were 84% and 76% respectively, while that of primary and secondary graft failure was 10% and 8% respectively. The 100-day CI of acute GvHD grade III-IV(95% CI) was 13%, while the 24-month CI of extensive chronic GvHD was 4%. After a median follow-up of 43.4 months, the 2-year overall survival(OS) and GvHD/Rejection-free Survival

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(GRFS) probabilities are 67% and 53%, respectively. The TCR $CD3^{+}\alpha\beta^{+}/CD19^{+}$ depletion group showed a significantly lower incidence of both acute and chronic GvHD and higher OS (79%; *p0.013*) and GRFS (71%; $p < .001$), while no significant differences in outcomes have been observed by different diagnosis and conditioning regimens. This large retrospective study supports the safety and feasibility of haplo-SCT in I-BMF patients. $TCR\alpha\beta^{+}/CD19^{+}$ depletion offers higher chances of patients' survival, with a significantly lower risk of severe a- and c-GvHD in I-BMFs compared to other platforms.

1 | INTRODUCTION

Inherited Bone Marrow Failure syndromes (I-BMFs) are a heterogeneous group of life-threatening genetic diseases that share a progressive decline of bone marrow function with variable risk of evolution to myelodysplastic syndrome and acute leukemia.[1,2] Some carry somatic abnormalities and a high risk of developing solid tumors.[3] Bone marrow failure usually starts in childhood[4] but occasionally may appear in adulthood and true I-BMFs are misdiagnosed as having "idiopathic aplastic anemia".[2] Several syndromes are well-described and genetically classified as I-BMFs, while other genetic disorders have been recently described as "overlapping" with primary immunoregulatory disorders.[5] In all of them, allogeneic hematopoietic stem cell transplantation (allo-HSCT) represents the only curative option for bone marrow failure.[6,7]

Over the years, the outcomes of allo-HSCT have been widely reported in most of the classic I-BMFs.[8–12] These studies revealed the importance of not delaying the transplant in the presence of worsening cytopenia; of performing it prior to malignant transformation, which significantly worsens the outcome[13]; and avoiding severe graft-versus-host disease (GvHD) that negatively affect survival, quality of life and the incidence of developing secondary malignancy.[14] However, one of the most relevant clinical challenges remains to establish the best approach in case of the absence of a matched family donor or a full-matched unrelated donor.

Haploidentical SCT (haplo-SCT) is currently considered the main alternative in these cases,[15,16] with parents usually readily available for stem cell donation, and building on the evolution of both ex-vivo and in-vivo T-cell depletion approaches which significantly improved the outcomes of haplo-HSCT in congenital diseases.[17,18] However, graft failure (GF) and GvHD remain the main concerns using T-depleted and unmanipulated grafts[17,18] respectively and the real-life data and outcome of haplo-HSCT in I-BMFs are currently lacking, with no evidence in favor of one type of T-cell depletion approach over the other.

In this retrospective study we describe the outcome of haplo-SCT in a large cohort of I-BMFs patients, comparing results based on the different diagnoses, conditioning regimens, and T-cell depletion approaches.

2 | MATHERIALS AND METHODS

2.1 | Study design and selection criteria

This retrospective study was conducted on behalf of the Severe Aplastic Anemia and Pediatric Diseases Working-Parties of the EBMT (EBMT SAAWP and PDWP). Data on patients registered with a diagnosis of classical I-BMFs (*Fanconi anemia-FA*, *Telomere Biology Disorders-TBDs*, *Diamond-Blackfan anemia-DBA*, *severe congenital neutropenia-SCN*, *Shwachman–Diamond syndrome-SDS*, *and congenital amegakaryocytic thrombocytopenia-CAMT*) who underwent haplo-SCT from 1990 to 2020 were collected from EBMT Registry. Additional data not included in the original EBMT Database were obtained by a specific questionnaire distributed to participating centers.

EBMT centres obtained informed consent according to the local regulations applicable at the time of transplantation in order to report pseudonymised data to the EBMT.

The primary objective was to report Overall Survival (OS) and GvHD/Rejection-free survival (GRFS). The secondary objectives were to compare outcomes by primary diagnoses, conditioning regimens and applied T-cell depletion (TCD) approaches, which were considered as the main potential influential variables.

2.2 | Definitions

Conditioning regimen was categorized as myeloablative conditioning (MAC) and no-myeloablative/reduced intensity conditioning (NMA/RIC) according to common definitions.[19] The latter group includes patients who received mini-TBI, defined as a low dose of total body irradiation (200–300 cGy).

Haplo-SCT platforms were categorized on the basis of T-cell depletion (TCD) approach, defining (1) "*ex vivo* TCD" those based on graft manipulation procedures performed with immunomagnetic microbeads-based method as the positive selection of $CD34^{+}$ cells ($CD34^{+}$ selected graft)[20–22] or negative selection of $TCR\alpha\beta^{+}$-$CD3^{+}$ and $CD19^{+}$ cells ($TCR\alpha\beta^{+}/CD19^{+}$-depletion),[18,23] as previously described; (2) "T-repleted with in vivo TCD" haplo-SCTs without any graft manipulation and based on the use of post-transplant Cyclophosphamide (PTCy)[24] or exclusively on ATG or Alemtuzumab

(ATG/Alem) administered to recipient in the context of conditioning regimen without PTCy.

Neutrophil and platelet engraftment were defined as the first of three consecutive days of achieving a sustained peripheral blood neutrophil count of >0.5 × 10^9/L[25] and as the first of at least 7 days with a platelet count of more than >20 × 10^9/L[26] without any transfusion during the 5 days before, respectively.

Primary graft failure (PGF) was defined as a failure to achieve a neutrophil count >0.5 × 10^9/L and secondary graft failure (SGF) was defined as a decrease of neutrophil counts to a level lower than 0.5 × 10^9/L after initial engraftment. Acute-GvHD and limited and extensive c-GvHD were scored according to previously reported criteria.[27,28] GRFS was defined as survival without acute-GvHD (a-GvHD) grade III-IV, extensive chronic-GvHD (c-GvHD), graft failure (GF)/rejection, relapse of a pre-transplant malignant transformation or a second transplant.

All outcomes in the study are defined from the time of the first allogeneic transplantation.

2.3 | Statistical analyses

OS and GRFS were estimated using the Kaplan–Meier product limit estimation method, and differences in subgroups were assessed by the Log-Rank test. The median follow-up time was determined using the reverse Kaplan–Meier method. Cumulative incidences (CI) of neutrophil engraftment and platelet recovery, grade II-IV and III-IV a-GvHD, c-GvHD, and graft failure were analyzed separately in a competing risks framework. For each of the outcomes, the competing events were no engraftment, graft loss, relapse, second transplant, and death. Subgroup differences in cumulative incidences were assessed by Gray's test. All estimates are reported with a corresponding 95% confidence interval in parentheses, and *p*-values <.05 were considered statistically significant. Statistical analyses were performed using the SPSS software, version 22 (SPSS Inc., Chicago, IL) and R statistical platform, version 3.0.3 (The R Foundation for Statistical Computing, Vienna, Austria) using packages "prodlim", "survival" and "cmprsk".

3 | RESULTS

3.1 | Patients' and transplants' characteristics

Data of 150 haplo-SCTs performed in patients with a diagnosis of classical I-BMF were collected from 56 centers affiliated with the EBMT network. The majority of haplo-SCTs were performed after 2012 (80%), with a median patient age at transplant of 8.8 years (IQR 6.2–11.4). Fanconi Anemia was the most frequent diagnosis ($n = 110$, 73.3%). Table 1 summarizes patient and transplant characteristics of the whole cohort. Characteristics stratified by different sub-diagnoses have been reported in Supplementary tables 1 and 2 and described in a specific section below. The NMA/RIC conditioning regimen was

TABLE 1 Patient and transplant characteristics at diagnosis and haplo-SCT.

	n	%
Diagnosis		
• Fanconi Anemia	110	*73.3*
• Congenital Amegakaryocytic Thrombocytopenia	14	*9.3*
• Diamond-Blackfan syndrome	9	*6*
• Dyskeratosis Congenita	9	*6*
• Shwachman-Diamond syndrome	6	*4*
• Dyserythropoietic anemia	1	*0.7*
• Congenital sideroblastic anemia	1	*0.7*
Haplo categories		
• TCRαβ+/CD19 + -depletion	63	*42.0*
• PTCy	52	*34.7*
• In vivo TCD (ATG/Alem)	23	*15.3*
• CD34+ selected graft	12	*8.0*
Stem cell source		
• BM	55	*36.7*
• PB	94	*62.7*
• BM + PB	1	*0.6*
Conditioning regimens		
• Flu-based	113	*77.4*
• *Flu-Cy*	*62*	
• *Flu*	*38*	
• *Flu-TT*	*2*	
• *Flu-Mel*	*4*	
• *Flu-Mel-TT*	*6*	
• *Flu-Cy-TT*	*1*	
• Bus-based	24	*16.4*
• Treo-based	9	*6.2*
• *Other*	*4*	-
Total body irradiation		
• 2 Gy	76	*51*
• No	73	*49*
• *Missing*	*1*	
Serotherapy		
• ATG	132	*88*
• Alemtuzumab	5	*3.3*
• None	13	*8.6*
Total haplo-HSCT	*150*	*100.0*

Abbreviations: ATG, Anti-thymocyte globulin; BM, bone marrow; Bus, Busulfan; Cy, Cyclophosphamide; Flu, Fludarabine; Mel, Melphalan; PB, peripheral blood; PT-Cy, Post-transplant cyclophosphamide; TT, Thiotepa; Treo, Treosulfan.

Fludarabine-based in 113 haplo-SCTs (77.4%), while MAC Busulfan- or Treosulfan-based conditioning was given in 33 (22.6%). A single dose of 2.0 Gray of total body irradiation (mini-TBI) was given in 51% ($n = 76$) of patients with haplo-SCT.

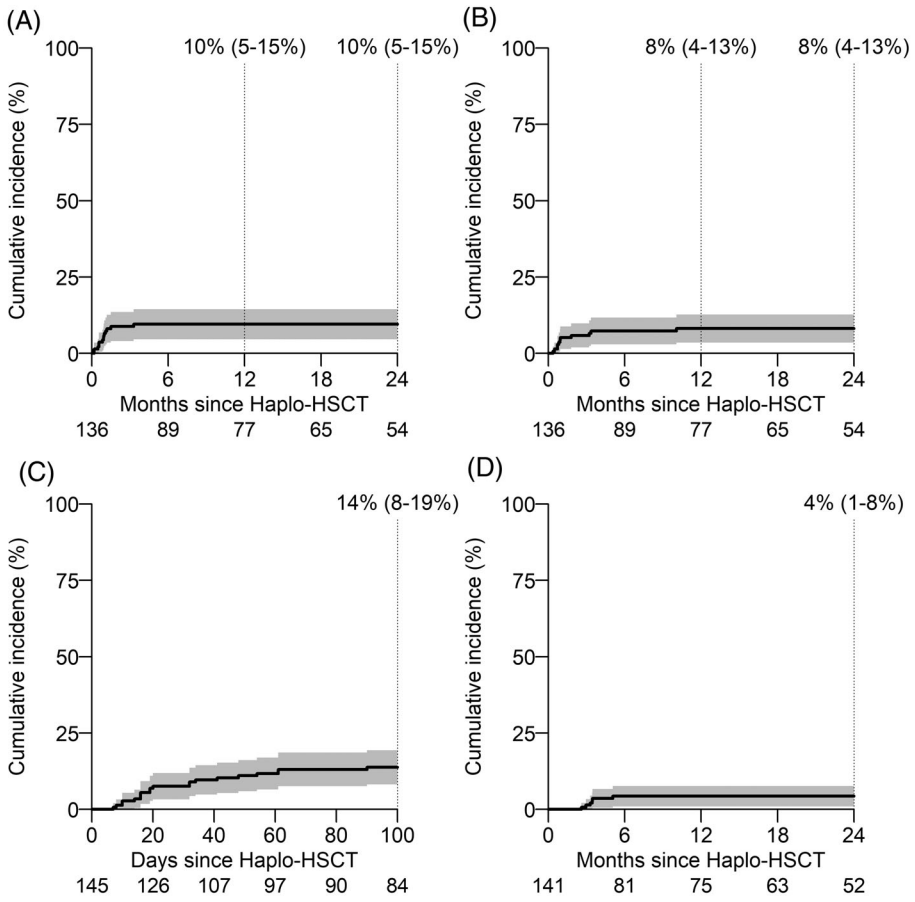

FIGURE 1 Cumulative incidences of (A) Primary Graft Failure, (B) Secondary Graft Failure (C) acute Graft versus Host disease (aGvHD) grade III-IV and (D) extensive chronic GvHD (cGvHD). Cumulative incidences are represented as percentages, with the 95% confidence intervals indicated as shaded regions. Below the time axis are the number of patients at risk at indicated timepoints. Specific cumulative incidences are given with confidence intervals, at timepoints indicated by the vertical dashed lines.

Among the 4 haplo-SCT platforms identified (Table 1), ex vivo TCD with TCR$\alpha\beta^+$/CD19$^+$-depletion ($n = 63$, 42%) and the T-repleted with in vivo TCD with PTCy ($n = 52$, 34.7%) approaches were the most frequently used, while T-repleted with in vivo TCD with ATG or alemtuzumab ($n = 23$, 15.3%) and ex vivo TCD with CD34$^+$-selection ($n = 12$, 8.0%) represented a minority.

All recipients in the PTCy group received post-transplant GvHD prophylaxis in addition to cyclophosphamide: cyclosporine (CyA) with mycophenolate (MMF) in 41 (78.8%), CyA alone in 6 (11.5%) and MMF with or without Sirolimus in the remaining 5 (9.6%). Similarly, a calcineurin-inhibitor (CyA or FK506) with MMF (15, 65.2%) or as a single agent (6, 6.1%) was administered in patients in the group of T-repleted with in vivo TCD ATG/alemtuzumab. On the contrary, all recipients of haplo-SCT with ex vivo TCD with CD34$^+$-selection did not receive any post-transplant GvHD prophylaxis, and neither did the majority of ex vivo TCD with TCR$\alpha\beta^+$/CD19$^+$-depletion ($n = 42$, 66.6%), while in the remaining patients CyA ($n = 11$, 17.5%) or MMF ($n = 8$, 12.7%) or Sirolimus ($n = 2$, 3.2%) was given as single agent.

3.2 | Engraftment, graft failure and Graft-versus-Host Disease

The median times to neutrophil and platelets engraftment were 14 (13, 14) days and 18 (15–21) days after transplant respectively, with a cumulative incidence of neutrophil engraftment by day 28 of 84% (77%–90%) and of platelets engraftment by day 100 of 76% (68%–83%). PGF was reported after 13 haplo-SCTs and SGF after 11 haplo-SCTs (1 year CI of PGF was 10% [5%–15%] and of SGF 8% [4%–13%]) (Figure 1A).

Among patients evaluable for GvHD, the day-100 CI of grade II-IV a-GvHD was 29% (22%–37%), and 14% (8%–19%) considering only grade III-IV. The 1-year CI incidence of c-GvHD was 9% (4%–14%) while 4% (1%–8%) were extensive type (Figure 1B,C).

3.3 | Survival and causes of death

At a median follow-up of 46.9 months (IQR 34.2–51.9), the 2-year OS was 66% (58%–74%) and the 2-year GRFS probability was 51% (43%–60%) (Figure 2A,B), resulting in a 5-year OS and GRFS of 65% (57%–73%) and 50% (42%–59%) respectively. Deaths occurred at a median time of 95 days after haplo-SCT (IQR 56–206). In the 52 patients who died within 2 years after SCT, the most frequent main causes of death were graft failure ($n = 17$, 32.7%) and GvHD ($n = 14$, 26.9%). In the remaining 21 patients the causes of death were infections ($n = 13$, 25%), toxicities and other SCT-related causes (Supplementary material 3).

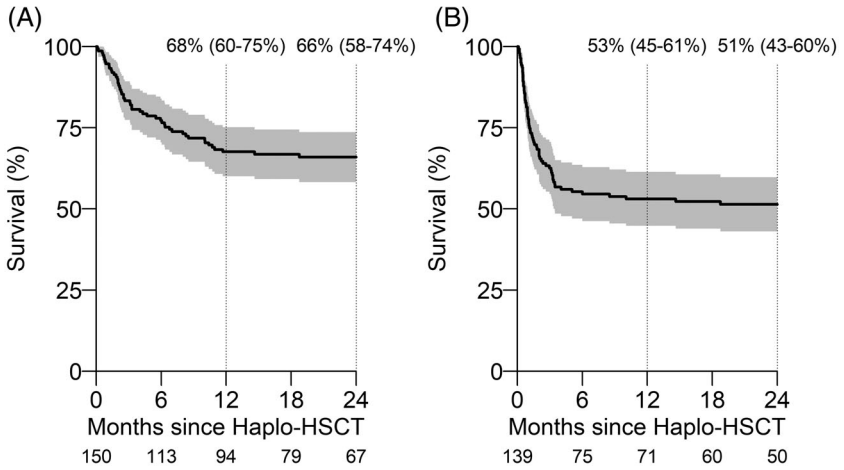

FIGURE 2 Kaplan–Meier curves of (A) Overall Survival and (B) Graft versus Host Disease/Rejection-free survival. Survival probabilities are represented as percentages, with the 95% confidence intervals indicated as shaded regions. Below the time axis are the number of patients at risk at indicated timepoints. Specific survival percentages are given with confidence intervals, at timepoints indicated by the vertical dashed lines.

TABLE 2 Univariable outcomes of overall survival (OS), Graft versus Host Disease/Rejection-free survival (GRFS), acute Graft versus Host Disease (aGvHD) II-IV, chronic GvHD (cGvHD) and primary and secondary graft failure, stratified by diagnosis and treatment characteristics.

		OS		GRFS		aGvHD II-IV (day 100)		cGvHD (2 y)		Graft failure			
										Primary		Secondary	
		%	*p*	%	*p*	%	*p*	%	*p*	%	*p*	%	*p*
Diagnosis	• Fanconi	66 (57–75)	.8	53 (44–63)	.5	31 (22–40)	.5	10 (4–15)	.9	9 (3–14)	.6	4 (0–8)	***.002***
	• Other	67 (52–82)		45 (28–62)		25 (11–39)		11 (1–22)		12 (1–23)		21 (7–35)	
Haplo categories	• PTCy	64 (51–77)	***.019***	45 (31–59)	***<.001***	43 (29–57)	***.005***	18 (8–29)	.06	6 (0–13)	***.05***	4 (0–10)	***.004***
	• TCRαβ$^+$/CD19$^+$ • Depletion	78 (67–88)		70 (58–82)		17 (7–27)		9 (2–16)		5 (0–11)		7 (0–14)	
	• CD34$^+$ • Selected graft	42 (14–70)		17 (0–38)		9 *(0–26)*		0 *(0–0)*		27 (1–54)		36 (8–65)	
	• In vivo TCD (ATG/Alem)	51 (30–72)		34 (13–55)		43 *(22–64)*		0 *(0–0)*		19 (2–36)		5 (0–15)	
Conditioning regimen	• Flu-based	69 (60–78)	.5	54 (44–63)	.8	30 (21–39)	.7	9 (3–14)	.2	7 (2–12)	.6	10 (4–16)	.3
	• Bus/Treo based	60 (43–77)		47 (29–65)		27 (11–42)		16 (3–29)		10 (0–21)		3 (0–10)	
Total body irradiation	• No	59 (47–71)	.15	43 (31–55)	.12	30 (19–41)	.9	8 (1–14)	.3	15 (7–24)	***.037***	9 (2–16)	.8
	• Yes	72 (62–82)		58 (47–70)		29 (18–39)		13 (5–20)		4 (0–9)		7 (1–13)	

Note: Kaplan–Meier estimates are given of OS and GRFS, with group differences tested by logrank tests, and cumulative incidences are given for all other outcomes, with group differences tested by the Gray test. All estimates are reported with 95% confidence intervals in parentheses.
Abbreviations: aGvHD, acute graft-versus-host disease, Alem, alemtuzumab, ATG, Anti-thymocyte globulin, Bus, Busulfan, cGvHD, chronic graft-versus-host disease, Flu, Fludarabine, PT-Cy, Post-transplant cyclophosphamide, Treo, Treosulfan.

3.4 | Impact of diagnosis and conditioning regimen

No significant differences in OS, GRFS and acute and chronic GvHD were observed between primary diagnoses of I-BMFs (Fanconi versus others: OS 66% [57%–75%] vs. 67% [52%–82%] $p = .8$, GRFS 53% [44%–63%] vs. 45% [28%–62%] $p = .5$, grade II-IV a-GvHD 31% [22%–40%] vs. 25% [11%–39%] $p = .5$, c-GvHD 10% [4%–15%] vs. 11% [1%–22%] $p = .9$). Fanconi Anemia was associated with significantly lower cumulative incidence of SGF compared to other diagnoses (4% [0%–8%] vs. 21% [7%–35%], $p = .002$), while no significant differences were observed in PGF.

Similarly, no impact was observed of the different conditioning regimens (NMA/RIC Fludarabine-based versus MAC Busulfan−/Treosulfan-based: OS 69% [60%–78%] vs. 60% [43%–77%] $p = .5$, GRFS 54% [44%–63%] vs. 47% [29%–65%] $p = .8$, grade II-IV a-GvHD 30% [21%–39%] vs. 27% [11%–42%] $p = .7$, c-GvHD 9% [3%–14%] vs. 16% [3%–29%] $p = .2$, PGF 7% [2%–12%] vs. 10 [0%–21%] $p = .6$, SGF 10% [4%–16%] vs. 3% [0%–10%] $p = .3$) (Table 2). The presence of mini-TBI in the context of the conditioning regimen was associated with a significantly lower cumulative incidence of PGF (4% [0%–9%] vs. 15% [7%–23%], $p = .037$), without any impact observed on the other outcomes.

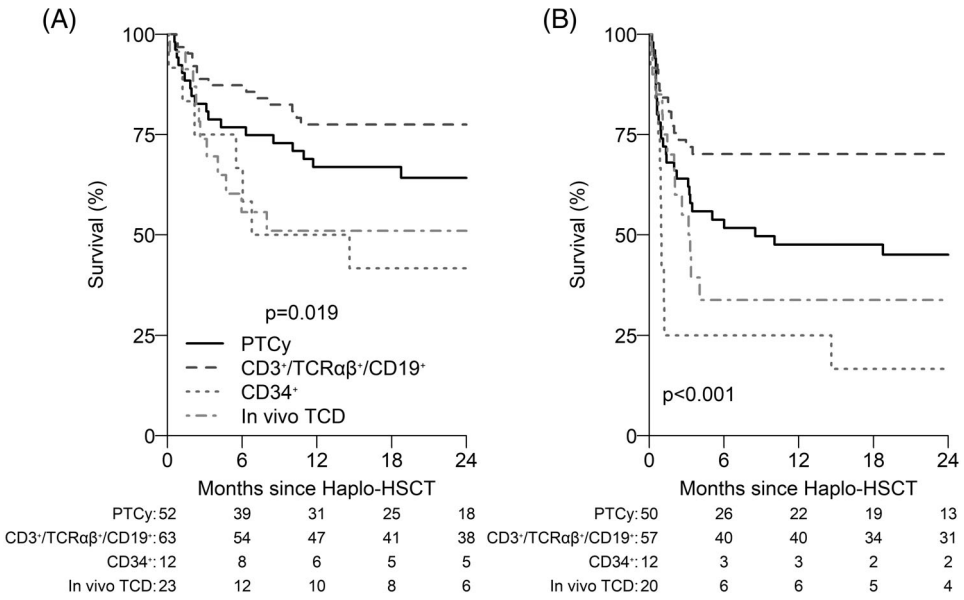

FIGURE 3 Kaplan–Meier curves of (A) Overall Survival and (B) Graft versus Host Disease /Rejection-free survival. Survival probabilities are represented as percentages. The corresponding log-rank *p*-value is indicated in the plot. Below the time axis are the number of patients at risk at indicated timepoints, in each group.

3.5 | Impact of different T-cell depletion approach

The comparison among the four T-cell depletion platforms showed that the specific approach impacted most of patient's outcomes. TCR-αβ-depletion and PTCy were associated with a significantly lower cumulative incidence of graft failure compared to other platforms (PTCy 10% [2%–19%], TCR-αβ-depletion 12% [4%–21%], CD34 64% [35%–92%], in vivo TCD with ATG or alemtuzumab 24% [6%–43%], $p < .001$), without significant differences observed between the first two groups.

Compared to PTCy, TCR-αβ-depletion led to a significantly lower incidence of grade II-IV acute GvHD (17% [7%–27%] vs. 43% [29%–57%], $p = .005$) and a trend in reduced incidence of chronic GvHD (9% [1%–16%] vs. 18% [8%–29%], $p = .06$) (Table 2).

This effect of TCR-αβ-depletion on short-term outcomes translates into higher 2-year-OS and 2-year-GRFS probability (78% [67%–88%] and 70% [58%–82%], respectively) compared to other platforms (64% [51%–78%] and 45% [31%–59%] with PTCy, 42% [14%–70%] and 17% [0%–38%] with $CD34^+$-selection and 51% [30%–72%] and 34% [13%–55%] with ATG/Alemtuzumab, $p = .019$ and $p < .001$) (Figure 3A,B).

3.6 | Focus on the different sub diagnoses: Fanconi Anemia and non-FA classical IBMFs

Fanconi Anemia was diagnosed in 110 patients. Among them, 11 (10%) had a malignant transformation before haplo-SCT (4 myelodisplastic syndrome and 7 acute myeloid leukemia). In this group, the most frequent haplo-platforms used were ex vivo TCD with $TCR\alpha\beta^+/CD19^+$-depletion ($n = 48$, 43.6%) and T-repleted with PTCy ($n = 39$, 35.5%) (Supplementary material 2). The majority of conditioning regimens were NMA/RIC Fludarabine-based ($n = 99$, 90%) and mini-TBI was added in 66 patients (60%). Of note, in the T-repleted with PTCy group, all patients with information available (23/39) received a reduced dose of post-transplant Cyclophosphamide equal to 25 mg/kg instead of the conventional dose of 50 mg/kg for 2 days.

Overall and in the subset of FA patients TCR-αβ-depletion proved to have a positive effect compared to other platforms, being associated with a significantly lower incidence of GF ($p = .004$) and aGvHD ($p = .046$) and consequently better OS ($p = .026$) and GRFS ($p = .007$). Conversely, in the group of FA patients, the reduced incidence of GF given by miniTBI translates into a significantly higher OS ($p = .031$) and GRFS ($p = .02$) (Supplementary material 1). Additionally, FA patients with malignant transformation before transplant, most of whom (72.7%) had active disease at the time of transplant, had a worse outcome in terms of lower 2-year-OS (transformed vs Not-transformed: 36% [8%–65%] vs. 69% [60%–78%] [p .01]).

The low number of non-FA patients in this cohort prevents further analyses in this group. However, in Supplementary material 3 their main features and outcomes are summarized.

4 | DISCUSSION

Upfront allo-SCT still represents the only curative option for patients with I-BMFs.[29] Haplo-SCT is the main alternative for patients without a healthy matched related or unrelated donor, and TCD mitigates the otherwise high risk of developing severe GvHD. However, historically haplo-SCT with TCD was burdened with a higher incidence of engraftment failure and a slow achievement of immune reconstitution, but the evolution in both ex vivo and in vivo TCD has changed the history of haplo-SCT in both malignant[30–32] and non-malignant diseases.[18] In particular, the introduction of column-based cell separation

techniques using microbeads conjugated magnetically with monoclonal antibodies,[33] which allows a highly efficient negative selection of alloreactive T-cells similar to TCRαβ+ T-cells depletion, represents a valuable step forward in ex vivo graft manipulation.[34,35] These appoaches guarantee a low risk of GvHD while promoting engraftment, effective infections management and, in leukemia patients, relapse prevention[36,37] by the persistence in the graft of several cell types like Natural Killer Cells (NK-cells) and TCRγδ+ T cells.[38]

Similarly, the introduction of PTCy in T-repleted haplo-SCT contributed to the reduced risk of GvHD due to the killing of emerging alloreactive T-cells in the first days after transplant,[39,40] preserving engraftment and immune reconstitution. In recent years, the safety and efficacy of both approaches has been demonstrated in children with congenital diseases[27,28,41–45] and also Fanconi Anemia,[46–49] with high survival reported. In lieu of evidence to favor one approach over the other there has been active debate overwhich approach carries more advantages.36,50

To the best of our knowledge, this is the largest cohort reporting outcomes of haplo-SCT in classical I-BMFs comparing different in vivo and ex vivo T-cell depletion approaches.

Our data show that haplo-SCT is a valid alternative for classical I-BMFs patients with indication for allogeneic transplant and lacking a fully matched donor. The overall long-term outcome reported in this heterogeneous group of diseases suggests that improvement is still required, since the 5-year estimates of OS (66%) and GRFS (52%) are not satisfactory, and the significant impact of graft failure and infections require a careful assessment. However, dissecting the sub-group analysis by TCD platform, it shows that TCRαβ$^+$/CD19$^+$ emerges as the most promising approach with significantly higher chances of survival, and a significantly lower risk of severe a- and c-GvHD compared with PTCy.

Furthermore, it appears that the impact of graft failure is significantly reduced with TCRαβ/CD19-depletion as well as with PTCy, reflecting progress in this respect.

These important findings will support challenging clinical decisions about how to manage haplo-SCT in I-BMFs and the choice of advanced graft manipulation. The selection bias in our cohort in which the most represented diagnosis is FA (70.1%) suggests that our conclusions are very likely applicable to FA patients, as confirmed by analysis focused on this group (Supplementary Material 1) but may need to be confirmed for other I-BMFs. Similarly, althought the lower survival rate observed in transformed Fanconi Anemia confirms our previous observation13 regarding the wrost outcome of trasformed-FA with active disease at time of transplant (any donor), this result should be confirmed in a larger population.

T-repleted haplo-SCT with PTCy is widely performed globally because of its low-cost and simplicity, which allows patients to access haplo-SCT also in resource-limited areas.51,52 In contrast, TCRαβ$^+$/CD19$^+$ depletion requires high expertise in ex vivo graft manipulation and cytofluorimetry evaluation with a higher cost of materials for cell manipulation making it harder to reproduce. Regardless of this important limitation, TCRαβ$^+$/CD19$^+$ depletion stands as the best option for I-BMFs due to the significantly reduced incidence of severe a- and c-GvHD and higher GRFS, at least in areas where advanced technologies are available, by securing higher chances of survival and higher quality of life.

Further, when the likely reduction in subsequent healthcare costs due to reduced severe GVHD are considered, the overall economic impact of haplo-SCT with the TCRαβ$^+$/CD19$^+$ depletion may be reduced,53 balancing out the initial cost of graft manipulation, so that it may result become cost-effective compared with other strategies. Pharmacoeconomic studies, currently lacking in HSCT, could support this hypothesis.

As for mini-TBI in the context of RICs, it seemed to reduce the incidence of PGF in our cohort. This positive effect did not show any impact on survival in the whole cohort, but its contribution is statistically significant within the group of FA patients. While further investigations are needed to better define the role of mini-TBI in this context, our data show that its addition in a RIC for haplo-SCT in FA contributes to a favorable outcome. In addition, a longer follow-up might reveal its potential impact on late effects such as the incidence of secondary tumors.

This study has limitations and strengths. The main limitations consist of the retrospective nature of the transplant registry-based study and the incompleteness of some items of the dataset, in particular related to other factors potentially impacting graft failure, such as graft composition and the recipient's donor-specific anti-HLA antibodies (DSA).54 These limitations, inherent to all retrospective registry studies, prevent more detailed analysis of the impact of different diagnoses on the risk of graft failure, which appears lower in FA compared to non-FA patients. In this regard, one might hypothesize that this effect could be due to the likely higher prevalence of alloimmunization in non-FA recipients with high transfusion dependence before transplantation, such as patients with DBA and CAMT. Furthermore, the characteristics of the bone marrow microenvironment could play a role in some of them, such as in Diskeratosis congenita, among whose patients graft failure has been diagnosed in the 83% (Supplementary Material 2). Further studies are required to investigate these hypotheses.

A further limitation is that while follow-up of almost 4 years confers robustness of the endpoints of this study, it is still insufficient to provide reliable data on the incidence of second tumors that represent the main late cause of death in Fanconi Anemia.55,56

The main strengths of this study is the large cohort size, particularly important for rare disorders like I-BMFs and the streamlined study design that offers an unique opportunity to address important questions in specific subgroups of patients regarding the different TCD platforms for haplo-SCT. These enable useful information to be derived for the clinical management of this very challenging situation.

Overall, our study suggests that for I-BMFs patients with a confirmed indication for allo-HSCT and lacking a fully matched donor, proceeding rapidly to a haplo-SCT is an acceptable option. If the expertise and technology are available, then TCRαβ$^+$depletion should be the preferred approach as this optimizes OS and GRFS. On the

other hand, T-repleted haplo-SCT with PTCy represents a valid alternative where graft manipulation is not feasible.

In the future, we hope to work towards developing a consensus for shared protocols for both T-replete and T-depleted haplo-SCT as well as initiating prospective studies in order to further define the best approach and improve outcomes in these diseases.

AUTHOR CONTRIBUTIONS

Stefano Giardino designed the research and wrote the paper; Régis Peffault de Latour, Antonio Risitano and Carlo Dufour contributed equally by designed the research and reviewed the paper; Brian Piepenbroek prepared database and managed contacts with participating centers; Dirk-Jan Eikema analyzed results and made the figures; all others authors reviewed the paper. All authors contribute equally in the data collection, each one for data related to patients from their own center.

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ACKNOWLEDGMENTS

The authors thank all the following investigators whose centres participated in this study: Persis Amrolia, Great Ormond Street Hospital Children's Charity, London, United Kingdom; Musa Karakukcu, Erciyes University, Faculty of Medicine, Kayseri, Turkey; José Mª Moraleda, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain; Jose Rifón, Clínica Universitaria de Navarra, Pamplona, Spain; Polina Stepensky, Hadassah University Hospital, Jerusalem, Israel; Amos Toren, Edmond & Lily Safra Children's Hospital, Tel-Hashomer, Israel; Akif Yesilipek, Medical Park Antalya Hospital, Antalya, Turkey; Josu de la Fuente, Division of Pediatrics, London, United Kingdom; Mahmoud Aljurf, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia; Peter Bader, Universitaetsklinikum Frankfurt Goethe-Universitaet, Frankfurt Main, Germany; Adriana Balduzzi, Centro Trapianto di Midollo Osseo - Clinica Pediatrica, Monza, Italy; Jacques-Olivier Bay, CHU ESTAING, Clermont, France; Bénédicte Bruno, Unité d'Hématologie Pédiatrique, Lille, France; Stefan Burdach, Klinikum Schwabing, Munich, Germany; Jenny Byrne, Nottingham University, Nottingham, United Kingdom; Alessandra Carotti, Sezione di Ematologia, Perugia, Italy; Cristina Diaz de Heredia, Hospital Vall d'Hebron, Barcelona, Spain; Franca Fagioli, Ospedale Infantile Regina Margherita, Torino, Italy; Jürgen Finke, University of Freiburg, Freiburg, Germany; Melissa Gabriel, The Children's Hospital at Westmead, Sydney, Australia; Marta Gonzalez Vicent, Niño Jesus Children's Hospital, Madrid, Spain; Amir Ali Hamidieh, Children's Medical Centre/Tehran University of Medical Sciences, Teheran, Iran, Islamic. Rose-Marie Hamladji, Centre Pierre et Marie Curie, Alger, Algeria; Yener Koc, Medicana International Hospital Istanbul, Istanbul, Turkey; Bruno Lioure, Techniciens d'Etude Clinique suivi de patients greffes, Strasbourg, France; Christine Mauz-Körholz, Justus-Liebig-University Giessen, Giessen,

Germany; Richard Mitchell, Sydney Children's Hospital, Sydney, Australia; Katharine Patrick, Sheffield Childrens NHS Foundation Trust, Sheffield, United Kingdom; Antonio Perez Martinez, Hospital Universitario La Paz, Madrid, Spain; Jaime Sanz, University Hospital La Fe, Valencia, Spain; Thomas Schroeder, University Hospital | Essen, Duesseldorf, Germany; Johanna Tischer, Klinikum Grosshadern, Munich, Germany; Estelle Verburgh, University of Cape Town Faculty of Health Sciences, Cape Town, South Africa; Robert F. Wynn, Royal Manchester Children's Hospital, Manchester, United Kingdom; Gülyüz Öztürk, Acibadem Saglik Hizm. ve Tic. A.S., Istanbul, Turkey. Open access funding provided by BIBLIOSAN.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest related to this study.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

PATIENT CONSENT STATEMENT

Participating centers obtained informed consent according to the local regulations applicable at the time of transplantation in order to report pseudonymized data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Giardino S, Eikema D-J, Piepenbroek B, et al. HLA-haploidentical stem cell transplantation in children with inherited bone marrow failure syndromes: A retrospective analysis on behalf of EBMT severe aplastic Anemia and pediatric diseases working parties. *Am J Hematol*. 2024;99(6):1066-1076. doi:10.1002/ajh.27293