ARTICLE

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Basic characteristics and safety of donation in related and unrelated haematopoietic progenitor cell donors – first 10 years of prospective donor follow-up of Swiss donors

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Since July 2007 prospective life-long follow-up (FU) for unrelated (URD) and related donors (RD) is mandatory in Switzerland and data on every allogeneic haematopoietic progenitor cell (HPC) donation are collected prospectively. We report the real-world experience of HPC donation during a 10-year study period (01.07.2007–30.06.2017) with basic characteristics and FU data. 1105 donors underwent 1155 HPC donation procedures. Eighty percent of first donations performed by 802 (73%) RDs and 303 (27%) URDs were peripheral blood stem cells (PBSC), 20% bone marrow (BM). Male donors were over-represented as URD (60% male vs 40% female). Main differences between RDs and URDs concerned age and pre-existing health disorders. RDs were significantly older at first donation (median age 48 years) compared to URD (34 years, $p < 0.0001$) and had more pre-existing health problems: 25% vs 9% in URD ($p < 0.0001$). No fatal complications occurred, collection related severe adverse events (SAE) after first donation were not significantly different between groups (RD 1.2%, URD 0.99%), incidence rates for neoplastic and autoimmune diseases did not exceed the rates of the general population. RDs are a more heterogeneous and potentially more vulnerable group, but if donor evaluation is performed appropriately, HPC donation is still safe.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) has become an established treatment for a wide range of acquired or congenital disorders. Because the probability of finding a suitable HLA-identical sibling donor in Switzerland is only about 30% [1], for the majority of patients a search for an unrelated volunteer donor (URD) is initiated in international registries with nearly 39 million donors registered worldwide [2].

Data on donor health and adverse effects collected mainly by the unrelated donor registries and other groups over the past 30 years have shown that severe adverse events (SAE) or fatal complications occur very rarely and that the initial fear of triggering or stimulating haematological or non-haematological malignancies by growth factors administered for peripheral blood stem cell (PBSC) mobilisation was proven unfounded [3–18].

Follow-Up (FU) of related donors (RD) is mandatory by FACT-JACIE standards since 2011, however monitoring, which is often still performed by the collection or transplantation centres, tends to be less consistent than for URD with comparatively scarce data on donor outcome.

Donor characteristics (age, eligibility criteria) differ considerably between RD and URD. Reliable answers to questions regarding donor safety or adequacy of eligibility assessment can only be obtained by prospective and consecutive collection and evaluation of large numbers of data from all donors without selection bias.

In this study, we analysed the first 10-year period of mandatory FU on related and unrelated donors in Switzerland. The goal of the study was firstly to describe and compare the characteristics and outcome of the two donor groups with focus on RD safety. Secondly, we summarise our experience with a standardised and centralised model of FU management for both URD and RD.

DONORS AND METHODS

Enactment of the new transplantation law on July 1st, 2007 made prospective life-long FU for all related and unrelated donors of hematopoietic progenitor cells (HPC) mandatory in Switzerland. Since then, data on every allogeneic HPC donation from an URD or RD in Switzerland are collected in the EBMT database ProMISe. All donors sign an informed consent.

FU procedures for RD and URD were standardised by the national registry for unrelated donors, Swiss Blood Stem Cells (SBSC) and the national professional organisation of transplant

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Table 1. HPC donations.

	Total	Related donors (RD)			Unrelated donors (URD)		
	Total	All RD (%)	PBSC (%)	BM (%)	All URD (%)	PBSC (%)	BM (%)
Donations, all	1155	847 (73.3)	683 (80.6)	164 (19.4)	308 (26.7)	243 (78.9)	65 (21.1)
1st donation	1105	802 (94.7)	648 (94.9)	154 (93.9)	303 (98.4)	240 (98.8)	63 (97.0)
2nd donation	44	40 (4.7)	31 (4.5)	9 (5.5)	4 (1.3)	3 (1.2)	1 (1.5)
3rd donation	6	5 (0.6)	4 (0.6)	1 (0.6)	1 (0.3)	0	1 (1.5)

centres, SBST (Swiss Blood Stem Cell Transplantation and Cellular Therapy). All FU procedures were coordinated by SBSC in collaboration with the 11 regional blood transfusion services (RBTS, which act as donor centres, where URD are registered and managed) for URD and the four national collection centres (CC, where the collections take place – all are situated in university hospitals) for RD. Between 2008 and 2012, 11 URD donated in an additional collection centre of a blood transfusion service. These donors were excluded from collection centre specific analyses. All collection facilities have been JACIE accredited since 2007 or before.

Number of donors and donations

Between 07/2007 and 06/2017, 1105 donors underwent 1155 HPC donation procedures, including 1105 first, 44 second and 6 third donations, all but one for the initial recipient (Table 1). Of all donations, 73.3% were performed by RD, 26.7% by URD. Around 80% of donations were PBSC and 20% BM. Furthermore, 54 lymphapheresis for donor lymphocyte infusions (DLI) were performed between 09/2013 and 06/2017 (Supplementary Table 1), ending up with a total number of 1209 donations.

Donations increased steadily over time except for URD BM and URD DLI (Supplementary Fig. 1). The vast majority of collections took place in three collection centres (CCs A, B, and C) while the fourth programme (D, paediatric) contributed 1.4% (13/926) of PBSC and 21% (48/229) of the BM collections (Supplementary Table 2).

Donor assessment

Donor assessments and the final decision on donor clearance were under the responsibility of collection centres' physicians with specific experience in evaluation and collection of HPC donors in consideration of the principle of divided responsibility [19, 20]. The evaluation of RD and URD followed the same procedure based on the currently valid quality standards and recommendations (WMDA; FACT-JACIE, national guidelines for URD).

As far as possible, the eligibility criteria for URD are applied for both groups. However, while donor safety is paramount for URDs and eligibility criteria are strictly adhered to, in real life RD with pre-existing health conditions that would have been deferred as URD might still undergo donation if these conditions are not expected to lead to a significant reduction in donor safety according to the judgement of the responsible physician.

RD often have a strong wish to donate and are willing to accept slightly higher risks, so that in certain situations RD are accepted for donation despite presenting medical issues.

Data collection and FU process

The FU process begins with the first injection of G-CSF in case of PBSC donation, the initiation of anaesthesia for BM donation and start of the apheresis procedure for DLI [21].

This study includes FU data on all donations performed between July 1st, 2007 and June 30th, 2017. As FU frequency was modified on September 1st, 2013, the data collection period is split into two parts. Period 1 covers the time from July 1st, 2007 until August 31st, 2013. The collected data include donor characteristics (age, gender, weight, relationship to patient), procedure related data (type of stem cell donation, number of donations, pre-existing health disorders, type and dosage of growth factors), any complication during and after collection and follow-up data. Data collection was at time of harvest, 1 month, 6 months, 1, 5, and 10 years post donation, then every 10 years.

Period 2 lasted from September 1st, 2013 until the end of the study period on June 30th, 2017. Based on the worldwide network for blood and marrow transplantation (WBMT) consensus statement [21], FU data collection was reduced to a minimal data set. That included limiting the recording of complications during and after donation to SAEs. SAEs are defined as death, life-threatening events, events entailing in-patient hospitalisation or prolongation of an existing hospitalisation due to WHO grade 3 or 4 toxicity or events that result in persistent or significant disability. ICD10 codes apply for description of medical problems. FU data focus on donor survival status, occurrence of any malignancy (haematological or non-haematological) and/or autoimmune disease.

Time-points of data collection beyond 1 year changed to FUs at 2, 4, 6, 8 and 10 years after donation. In period 2, we also began data collection on DLI donations. The FU procedure was basically the same in the two periods. The CC contacted donors a few days after donation to check on their immediate recovery. For the 1 month FU, donors were invited either to the collection centre (RD and since period 2 also URD) or the RBTS (URD during period 1), where they were seen by a physician and a blood count was performed.

From 6 months onwards, FUs for URD were performed either by SBSC for all donors registered in the SBSC donor centre (DC), or by the respective RBTS. For RD, FU initially took place in the collection centres, but was progressively transferred to SBSC. At these routine paper-based FU checks, donors were asked to note any medical problem on a FU questionnaire sent by post, which was reviewed by qualified staff on return. If necessary, the physician contacted the donor by phone for more information and/or initiated further examinations or treatment.

Data collection for this analysis was closed by the end of August 2017 to allow for all 30 day FUs (for donation procedures up until June 30th, 2017) to be captured.

Although SBSC is bound by law to conduct FU, donors are free to opt out of the procedure. If a donor has left two consecutive FUs unanswered or the registry has been unable to contact her/him for 2 years, the donor is declared 'lost to FU'.

Data analysis

Categorical variables were expressed as frequencies, whereas continuous variables were expressed as medians and ranges. Categorical data were compared by the Fisher exact test. Continuous variables were compared using the Wilcoxon–Mann–Whitney test. All reported P values are 2-sided. P-values < 0.05 were considered statistically significant for single comparison, $p < 0.01$ for multiple comparisons.

RESULTS

Donor characteristics

Counting all 1209 donations, 53.3 % were made by male and 46.7% by female donors. Among RD, female (439, 49.2%) and male

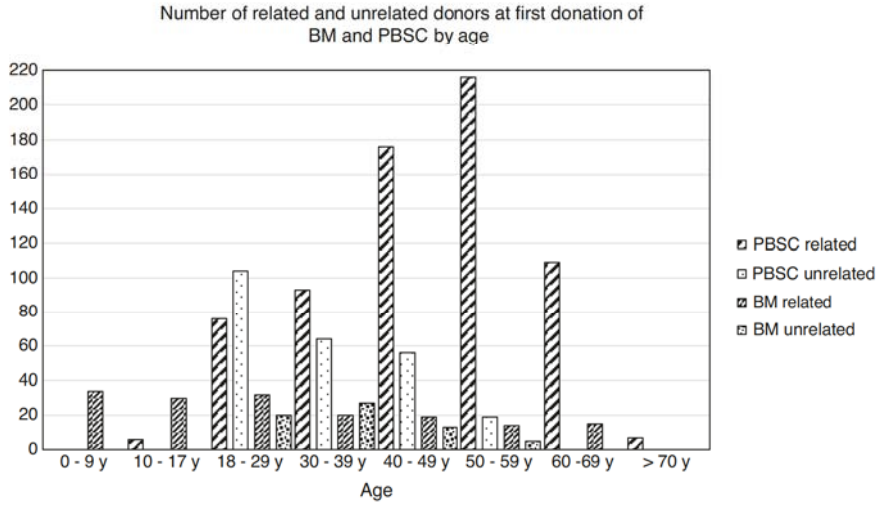

Fig. 1 Number of related and unrelated donors at first donation of BM and PBSC by age. At the time of first donation, 69% of all unrelated PBSC donors were below the age of 40 years ($n = 166$) and 43% ($n = 103$) between 18 and 29 years old. None of the URD was older than 60 years (upper age limit for URD). In contrast, 75% of the related PBSC donors were ≥ 40 years ($n = 485$), 49% ($n = 320$) were ≥50 years old with 17% ($n = 111$) being 60 or older, including seven donors over 70 years of age. Eight percent ($n = 67$) of RDs were donors <18 years of age, 62 donated BM, 5 PBSC.

donors (454, 50.8%) were practically equally distributed while male donors were predominant among URD (60.1% vs 39.9% female donors, $p = 0.003$). Gender distribution remained stable among PBSC and BM donations (Supplementary Table 3).

Median age at first donations was 48 years (IQR 34–57 years) in RD and 34 years (IQR 25–42 years) in URD ($p < 0.0001$) with remarkable differences in the age distribution between RD and URD (Fig. 1). Among PBSC donors, median age in RD was 49 years (IQR 40–58 years) and 32 years (IQR 25–42 years) in URD ($p < 0.0001$). Median age of related BM donors was lower than in URDs (23 years, IQR 13–45 versus 34 years, IQR 27–42, $p = 0.0004$) with 40% of RD BM collections being performed on minors between 6 months and 18 years of age (Supplementary Table 4).

Approval of G-CSF for PBSC mobilisation in paediatric donors differs among countries and, therefore, also PBSC donation in healthy paediatric donors [22, 23]. In Switzerland, filgrastim is authorised for PBSC mobilisation in healthy donors without age restriction but only six paediatric donors (aged 12–17 year, weight 38–83 kg) donated PBSC without any short- or long-term complications.

In total, 192 RD (24%, 192/802) were outside the age limit for URD at first donation: 125 RD were ≥60 years (15.6%), 67 < 18 years (8.4%), and 610 were aged 18–59 years (76%).

Pre-existing health disorders

At first donation, one or more pre-existing health disorders were significantly more frequent in RD than in URD (283 disorders in 197/802 donors (25%) versus 31 disorders in 27/303 donors (9%); $p < 0.0001$; Table 2). The proportion increased with age of the donor (<18 years: 10%, 18–59 years: 21%, ≥60 years: 49%). Among RD a number of donors had more than one health disorder: 24% (47/197) indicated two, 6.5% (13/197) three or four health disorders. A large variety of different entities was detected with circulatory, endocrine/metabolic, haematological and genito-urinary disorders being significantly more frequent in RD (Supplementary Table 5). Vascular risk factors such as arterial hypertension and dyslipidaemia were significantly more frequent in RD with a further trend for diabetes and hypothyroidism. Overall, we estimate that in 49 cases (6.1%), the medical issue would have caused donor deferral as URD. Of the 67 under-aged donors, seven had pre-existing health disorders that did not compromise their suitability to donate. Among 125 RD aged 60 years and more, 61(49 %) had medical issues, which would potentially have caused deferral as URD in 17 cases (17/61, 28%). Eleven of them were female (65%), 6 male (35%). Among 610 RD within the age range for URD, 32 (5.2 %) had health disorders inacceptable for unrelated donation (Supplementary Table 6). No SAE was reported for any of these donors in the long-term FU.

Table 2. Pre-existing health disorders at first donation.

Disorders	RD, $n = 283$ (%)	URD, $n = 31$ (%)
Circulatory system	86 (30.4)	6 (19.4)
Endocrine & metabolic	55 (19.4)	5 (16.1)
Haematologic	28 (9.9)	0
Pulmonary	18 (6.4)	7 (22.6)
Psychiatric	17 (6.0)	2 (6.4)
Genito-urinary	11 (3.9)	0
Gastro-intestinal, liver	12 (4.2)	2 (6.4)
Neurological	11 (3.9)	3 (9.7)
Autoimmune	10 (3.5)	2 (6.4)
Oncological	7 (2.5)	0
Other	28 (9.9)	4 (13.0)

PBSC mobilisation and collection procedures

Filgrastim was most frequently used for PBSC mobilisation in 502 RD (73.4%) and 198 URD (81.5%), followed by Lenograstim in 161 RD (23.6 %) and 45 URD (18.5%). In 19 RD G-CSF was not further specified. No biosimilars were used during this period. Most donors donated by peripheral venous access (89.6% of RD and 92.2% of URD). Central venous catheters (CVC) were placed by experienced anaesthesiologists in 71 RD and 19 URD (10.4% vs 7.8%; $p = 0.2$) - subject to the donor's consent - if the collection was judged to be unfeasible via peripheral venous access by the CC physicians. The percentage is within the range in the literature (up to 20%) [6], but lower rates are achievable by more stringent deferral due to inadequate peripheral venous access [5, 24]. Need for CVC was significantly higher for female donors in both donor groups (14% of related and 17% of unrelated female donors versus 6% of related and 1% of unrelated male donors, $p < 0.0001$) (data not shown). Ultrasound guided peripheral venous access might help to decrease the need for CVC and is increasingly used in recent years.

BM collection procedures

Overall, 229 bone marrow collections were performed with 217 first donations (Table 1). Five RD (3.25%) and two URD (3%) underwent epidural anaesthesia. None of the procedures was terminated prematurely. Autologous blood donation was performed by 34 (21%) RD and 40 (62%) URD prior to BM collections. Most donors had the donated blood re-infused after donation (RD 94% and URD 92.5%). Over the years, the practise of collecting autologous blood prior to BM donation has decreased dramatically and is nowadays practically abandoned, similar to other reports [25]. Except for one paediatric donor, no donor received an allogeneic blood transfusion. This transfusion was linked to a known medical condition with secondary anaemia after collection.

Immediate/short-term SAE associated with the donation procedure

Overall, 13 SAEs were reported in association with the donation procedure (Table 3), concerning 10 RD (3 BM, 7 PBSC donors) and 3 URD (all PBSC donors), which amounts to 1.2% of RD and 0.99% of URD at first donation. There was no significant difference between RD and URD or among PBSC and BM donors ($p = 0.91$). Among 643 PBSC RD 4 SAE occurred in 532 donors (0.7%) aged 18–59 years and 3 SAE in 111 donors (2.7%) aged ≥60 years, resulting in a non-significant trend ($p = 0.07$) for a higher rate of SAE in the ≥60-year-old donors. Among 154 BM RD, 62 were ≤18 years of age with 2 SAE occurring in donors <1year and 1 SAE in a 60-year-old donor. There was no difference in SAE incidence between BM RD between 18–59 years or donors below or above this age range.

Seven SAE led to hospitalisation or prolongation of hospitalisation while others had the potential for more serious outcome (Table 3). In all of them, a close temporal relationship to the donation procedure exists so that a causal relationship is reasonable. In 3 PBSC RD pre-existing comorbidities might have contributed to the SAE (arterial hypertension, gastro-esophageal reflux disease, ventricular extrasystoles).

Neoplastic and autoimmune long-term events after first donations

During 4312 person-years of follow-up (2736 for RD and 1576 for URD) 12 neoplasms and 6 autoimmune diseases were observed in RD as well as one neoplasm and two autoimmune disorders in the URD group from 6 months post-donation onwards (Table 4). The neoplasm incidence rate for RD was 4.3/1000 person-years of FU including two cases of MGUS and basal cell carcinoma each. Since these neoplasms are not included in Swiss cancer registries we also calculated the incidence rate for RD without these events, resulting in 2.9/1000 person-years of FU. Neoplasm incidence rate for URD was 0.6/1000 person-years of FU. Both rates compared favourably with the incidence rate of 5/1000 person-years reported for the general Swiss population adjusted for age and sex. In two donors, personal history at collection was positive for basal cell carcinoma and meningioma (suspected). We refrained from more formal comparisons because numbers of events were low and the representative comparison group has still to be defined. RD may have a predisposition for malignancies but they undergo a rigorous medical check-up before donation that might lead to a positive selection. This hypothesis still needs to be investigated for RD while data from a large NMDP-study in URD have shown a lower cancer incidence in PBSC donors than in the general population [26].

The incidence rate for autoimmune disorders was 2.2/1000 person-years in RD and 1.3/1000 person-years in URD, including a variety of different diagnoses. Again, the number of events was low and not increased compared with the incidence rates for autoimmune disorders in the Swiss population as far as they are known. After careful analysis, none of the neoplasms or autoimmune diseases was considered causally related to the donation procedure. Six RD had other medical issues at donation

Table 3. Immediate/short term SAE associated with the donation procedure, first donations.

	SAE	Time of detection	gender	age	comorbidity
PBSC RD					
1	Arterial hypertension**	Start/during apheresis	female	54	known arterial hypertension
2	Angioedema*	During collection	female	60	none
3	Chest pain**	During collection, ECG and cardiac biomarkers uneventful, most likely due to GERD	male	52	arterial hypertension, dyslipidaemia, GERD
4	Hypocalcaemic tetany*	During collection	female	53	none
5	Severe musculoskeletal pain**	During mobilisation	male	67	HTA, prostate hyperplasia
6	Takayasu arteritis*	1 month after donation	female	54	asthma
7	Ventricular arrhythmia*	During collection	male	64	known extrasystoles, previous treatment for tachycardia 14 years earlier
BM RD					
1	Bilateral deep vein thrombosis*	2 days after collection	female	60	none
2	Broncho-/laryngospasm during intubation*	During intubation	female	6 mo	none
3	Fever, need for antibiotics**	Day 1 after collection	male	7 mo	none
PBSC URD					
1	Chest oppression after collection**	2 h after collection	male	35	none
2	Vestibular symptoms**	Days 3 and 4 of G-CSF mobilisation (before collection)	female	34	migraine
3	Acute appendicitis**	After 2 doses of G-CSF, (donated PBSC later after appendectomy)	female	21	none

*events with potential for more serious outcome.
**events that lead to hospitalisation or prolongation of hospitalisation.

Table 4. Late SAE in RD and URD from 6 months onwards for neoplastic and autoimmune disorders.

	FU	SAE	source	interval donation-diagnosis (months)	gender	age at donation	HLA match	Pre-exisiting medical problem at collection
URD	2 y	clinically isolated syndrome (CIS)	BM	16	female	26	unrelated donor	No
	4 y	seroneg. arthritis	BM	5	female	53	unrelated donor	No
	8 y	digital papillary adenocarcinoma	PB	60	male	35	unrelated donor	No
RD	6mo	MGUS	PB	6	female	55	ident. sibling	No
	1 y	asthma	PB	11	male	61.5	syngeneic	No
		melanoma	PB	11	male	65.8	syngeneic	depression,memory and concentration deficits after head trauma
		breast cancer	PB	12	female	66.5	ident. sibling	hypertension
		ulcerative colitis and autoimmune thyroiditis	PB	7	male	58.5	ident. sibling	vasovagal syncope at donation
		prostate cancer	BM	11	male	67.4	mismatched related	tinnitus
	2 y	prostate cancer	PB	20	male	52	ident. sibling	No
		asthma	PB	20	male	22.5	ident. sibling	No
	4 y	basalioma	PB	47	male	48.7	ident. sibling	No
	5 y	basalioma	PB	58	female	70	ident. sibling	history of basalioma at collection,pancreas insufficiency, nodular goiter
		MGUS	BM	63	female	44.9	ident. sibling	No
		glioblastoma	PB	60	male	52	ident. sibling	No
	6 y	Sjögren syndrome	PB	72	female	55.4	ident. sibling	No
		menigioma	PB	64	male	53.7	ident. sibling	already suspected at time of collection – progression and surgery 7 years after donation
	8 y	Crohn's disease	PB	84	male	46.4	ident. sibling	No
		prostate cancer	PB	96	male	54	ident. sibling	No
		Multiple myeloma	PB	83	female	58.4	ident. sibling	hypothyroidism
	10 y	Sjögren syndrome	PB	120	male	51.4	syngeneic	No

that had no connection with the later SAE. None of the RD with a history of malignancy reported a new event during follow-up except for one donor with basal cell carcinoma.

No malignancies or autoimmune disorders were reported for paediatric donors.

Among the 610 RD aged 18–59 years, 13 donors (12/532 PBSC and 1/78 BM donors) reported 14 SAE (one PBSC donor with two autoimmune disorders) during long term follow-up and five donors with long-term SAE were reported among 125 RD aged ≥60 years (4/111 PBSC and 1/14 BM donors).

A trend for a higher incidence rate in the older age group was not statistically significant and needs to be reanalysed in the future with higher numbers.

Performance of follow-up

Availability of follow-up reports for URD was 98% after 1 month, around 90% during the first year and mostly above 80% during the following years (Supplementary Table 7, Supplementary Fig. 2). These data compare favourably with other groups [5].

For RD, the return rate was generally lower with 87% follow-up after 1 month, around 65% during the first year and between 34–56% later on. Initially, CC were responsible for FU. Because of limited resources, FU was transferred to the registry from 2012 onwards, leading to a significant improvement of return rate (Supplementary Fig. 3) comparing favourably with other reports [8, 17, 27]. Overall, 91% of RD had at least one FU, 69.6% at least two FU during the first year of FU.

Overall, 60 RD and 4 URD had to be classed as 'lost to FU', 38 (4.7%) RD and 2 URD (0.6%) in the course of the first year. Reasons were either the donor's wish, residence in a foreign country, donor being untraceable or not responding.

DISCUSSION

Data on HPC donation from RD and URD were prospectively collected over a 10-year period (2007–2017) in Switzerland. This includes every consecutive donor who donated HPC during this period and therefore enables us to capture the fundamental differences in donor characteristics of both groups in terms of age, state of health prior to donation, eligibility criteria and their application, donation procedures, and short- and long-term follow-up.

The two main differences between RD and URD were donor age and state of health prior to donation. The data reveal a much wider age range for RD than for URD, contrasting age distribution and a substantially larger ratio of PBSC donors aged 50 or older at first donation in RD. The resulting 17 years' higher median age of related PBSC donors and 11 years' lower median age of related BM donors is linked to the lack of a strict age limit for related donors and the increase of older patients with consequently older sibling donors and a high proportion of BM donations among underage siblings [27–30]. In the real world, comorbidities are more frequent in RD, increase with age and would have caused deferral as URD in almost one third of RD over 60 years of age. These findings confirm the reports from the RDSafe study [27]. However, the donation is still safe. SAEs discovered by our short-term follow-up analysis (1.2% in RD and 0.99% in URD) are in the same range (1–2%) as reported by other groups [3, 4, 7, 8, 23, 26]. This shows that collections can be done safely despite slightly less stringent suitability criteria being accepted in some cases - with the donors' consent - provided risk assessment, selection and management of RDs is conducted appropriately [31, 32]. Both divided responsibility [19, 20] and involvement of physicians with specific experience in evaluation and collection of HPC donors for donor assessment are in our view essential for donor safety. Basically, RD should follow the same screening recommendations as URD as has been suggested by WBMT recommendations [31, 32]. Donations by donors not meeting URD eligibility criteria should be the exception but may be possible and safe after careful donor assessment that may require additional consultations.

We did not observe an increased age-adjusted incidence rate for malignancies or autoimmune disorders compared to the general population. No impact of pre-existing comorbidities on long-term donor safety could be observed as the RD suffering later malignancy or autoimmune disease either had no pre-existing health disorder at collection or there was no feasible connection between the reported comorbidity and a later event. However, limitations in our study restrict these analyses. We have no information on the state of health of donors after dropping out of FU and number of donors reaching the 8 or 10-year FU is still scarce. Hence, we might have missed events that neither became aware to the donor centres via family members nor patients. Since the observed number of malignancies and autoimmune diseases is low, huge datasets are necessary in order to detect an age-adjusted increased incidence rate for single entities. Given the pronounced differences in basic characteristics among related BM and PBSC donors the most appropriate control group for PBSC RD might be siblings who did not donate PBSC but would have been eligible to do so instead of the general population. Our data do not allow this kind of analysis.

HPC donation is generally considered medically safe for paediatric sibling donors [22, 23, 29, 30, 33, 34]. Our follow-up study did not reveal any SAE among 67 donors under 18 years. Furthermore, several reports indicate that follow-up procedures should be adapted to include also psychosocial late effects [35–38].

Finally, a high rate of complete follow-up reports is a basic prerequisite for donor outcome analysis. This is the first study to map allogeneic HPC donation over a 10-year period as it stands and to report on the set-up of a standardised, centralised FU procedure for both related and unrelated donors on a national basis. The study shows that such a process is feasible and applicable to both donor groups. In our hands, coordination and centralisation of follow-up by the unrelated donor registry was helpful to increase the follow-up rate. Still, RD follow-up is more challenging either because RDs living abroad (approx.15%) can be difficult to contact and having to communicate in a foreign language or via the recipient can be an additional hindrance. In our experience, many RD greatly appreciate the contact with the FU team, demonstrating the importance to provide them with a space for themselves where they can voice their concerns, should the need be [39, 40].

DATA AVAILABILITY

The datasets supporting the conclusions of this article are included within the article and its additional files.

REFERENCES

1. Tiercy J-M. How to select the best available related or unrelated donor of hematopoietic stem cells? Haematologica. 2016;101:680–7.
2. Website: https://statistics.wmda.info/ accessed on Dec 16th, 2021
3. Miller JP, Perry EH, Price TH, Bolan CD, Karanes C, Boyd TM, et al. Recovery and safety profiles of marrow and PBSC donors: experience of the national marrow donor program. Biol Blood Marrow Transplant. 2008;14:29–36.
4. Halter J, Kodera Y, Ispizua AU, Greinix HT, Schmitz N, Favre G, et al. Severe events in donors after allogeneic hematopoietic stem cell donation. Haematologica. 2009;94:94–101.
5. Hölig K, Kramer M, Kroschinsky F, Bornhauser M, Mengling T, Schmidt AH, et al. Safety and efficacy of hematopoietic stem cell collection from mobilized peripheral blood in unrelated volunteers: 12 years of single-center experience in 3928 donors. Blood. 2009;114:3757–63.
6. Pulsipher MA, Chitphakdithai P, Logan BR, Shaw BE, Wingard JR, Lazarus HM, et al. Acute toxicities of unrelated bone marrow versus peripheral blood stem cell donation: results of a prospective trial from the National Marrow Donor Program. Blood. 2013;121:197–206.
7. Pulsipher MA, Chitphakdithai P, Miller JP, Logan BR, King RJ, Rizzo JD, et al. Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor Program. Blood. 2009;113:3604–11.

8. Kodera Y, Yamamoto K, Harada M, Morishima Y, Dohy H, Asano S, et al. PBSC collection from family donors in Japan: a prospective survey. Bone Marrow Transplant. 2014;49:195–200.
9. Shaw BE, Confer DL, Hwang W, Pulsipher MA. A review of the genetic and long-term effects of G-CSF injections in healthy donors: a reassuring lack of evidence for the development of haematological malignancies. Bone Marrow Transpl. 2015;50:334–40.
10. Szer J, Elmoazzen H, Fechter M, Hwang W, Korhonen M, Miller J, et al. Safety of living donation of hematopoietic stem cells. Transplantation. 2016;100:1329–31.
11. Burns LJ, Logan BR, Chitphakdithai P, Miller JP, Drexler R, Spellman S, et al. Recovery of unrelated donors of peripheral blood stem cells versus recovery of unrelated donors of bone marrow: a prespecified analysis from the phase III blood and marrow transplant clinical trials network protocol 0201. Biol Blood Marrow Transplant. 2016;22:1108–16.
12. Schmidt AH, Mengling T, Hernández-Frederick CJ, Rall G, Pingel J, Schetelig J, et al. Retrospective analysis of 37,287 observation years after peripheral blood stem cell donation. Biol Blood Marrow Transplant. 2017;23:1011–20.
13. Kennedy GA, Morton J, Western R, Butler J, Daly J, Durrant S. Impact of stem cell donation modality on normal donor quality of life: a prospective randomized study. Bone Marrow Transpl. 2003;31:1033–5.
14. Shaw BE, Chapman J, Fechter M, Foeken L, Greinix H, Hwang W, et al. Towards a global system of vigilance and surveillance in unrelated donors of haematopoietic progenitor cells for transplantation. Bone Marrow Transpl. 2013;48:1506–9.
15. Favre G, Beksaç M, Bacigalupo A, Ruutu T, Nagler A, Gluckman E, et al. Differences between graft product and donor side effects following bone marrow or stem cell donation. Bone Marrow Transpl. 2003;32:873–80.
16. Martino M, Console G, Dattola A, Callea I, Messina G, Moscato T, et al. Short and long-term safety of lenograstim administration in healthy peripheral haematopoietic progenitor cell donors: a single centre experience. Bone Marrow Transpl. 2009;44:163–8.
17. De La Rubia J, de Arriba F, Arbona C, Pascual MJ, Zamora C, Insunza A, et al. Follow-up of healthy donors receiving granulocyte colony-stimulating factor for peripheral blood progenitor cell mobilization and collection. Results of the Spanish Donor Registry. Haematologica. 2008;93:735–40.
18. Anderlini P, Champlin R. Biologic and molecular effects of granulocyte colony-stimulating factor in healthy individuals: recent findings and current challenges. Blood. 2008;111:1767–72.
19. O'Donnell PV, Pedersen TL, Confer DL, Rizzo JD, Pulsipher MA, Stroncek D, et al. Donor health and safety working committee from center for international blood and marrow transplant research (CIBMTR). Practice patterns for evaluation, consent, and care of related donors and recipients at hematopoietic cell transplantation centers in the United States. Blood. 2010;115:5097–101.
20. van Walraven SM, Nicoloso-de Faveri G, Axdorph-Nygell UA, Douglas KW, Jones DA, Lee SJ, et al. WMDA Ethics and Clinical working groups. Family donor care management: principles and recommendations. Bone Marrow Transpl. 2010;45:1269–73.
21. Halter JP, van Walraven SM, Worel N, Bengtsson M, Hägglund H, Nicoloso de Faveri G, et al. Allogeneic hematopoietic stem cell donation—standardized assessment of donor outcome data: A consensus statement from the Worldwide Network for Blood and Marrow Transplantation (WBMT). Bone Marrow Transpl. 2013;48:220–5.
22. Pulsipher MA, Levine JE, Hayashi RJ, Chan KW, Anderson P, Duerst R, et al. Safety and efficacy of allogeneic PBSC collection in normal pediatric donors: the pediatric blood and marrow transplant consortium experience (PBMTC) 1996–2003. Bone Marrow Transpl. 2005;35:361–7.
23. Styczynski J, Balduzzi A, Gil L, Labopin M, Hamladji R-M, Marktel S, et al. Risk of complications during hematopoietic stem cell collection in pediatric sibling donors: a prospective European Group for Blood and Marrow Transplantation Pediatric Diseases Working Party study. Blood. 2012;119:2935–42.
24. Bräuninger S, Thorausch K, Luxembourg B, Schulz M, Chow KU, Seifried E, et al. Deferral of volunteer stem cell donors referred for evaluation for matched-unrelated stem cell donation. Bone Marrow Transpl. 2014;49:1419–25.
25. Kim-Wanner SZ, Luxembourg B, Schmidt AH, Schäfer R, Möller N, Herbert E, et al. Introduction of principles of blood management to healthy donor bone marrow harvesting. Vox Sang. 2020;115:802–12.
26. Pulsipher MA, Chitphakdithai P, Logan BR, Navarro WH, Levine JE, Miller JP, et al. Lower risk for serious adverse events and no increased risk for cancer after PBSC vs BM donation. Blood. 2014;123:3655–63.
27. Pulsipher MA, Logan BR, Chitphakdithai P, Kiefer DM, Riches ML, Rizzo JD, et al. Effect of aging and predonation comorbidities on the related peripheral blood stem cell donor experience: report from the related donor safety study. Biol Blood Marrow Transplant. 2019;25:699–711.
28. Passweg JR, Baldomero H, Bader P, Bonini C, Duarte RF, Dufour C, et al. Use of haploidentical stem cell transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report. Bone Marrow Transpl. 2017;52:811–7.
29. Passweg JR, Baldomero H, Bader P, Basak GW, Bonini C, Duarte R, et al. Is the use of unrelated donor transplantation leveling off in Europe? The 2016 European Society for Blood and Marrow Transplant activity survey report. Bone Marrow Transpl. 2018;53:1139–48.
30. Anderlini P. Sixty as the new forty: considerations on older related stem cell donors. Bone Marrow Transpl. 2017;52:15–9.
31. Worel N, Buser A, Greinix HT, Hägglund H, Navarro W, Pulsipher MA, et al. Suitability criteria for adult related donors: a consensus statement from the worldwide network for blood and marrow transplantation standing committee on donor issues. Biol Blood Marrow Transplant. 2015;21:2052–60.
32. Bitan M, van Walraven SM, Worel N, Ball LM, Styczynski J, Torrabadella M, et al. Determination of eligibility in related pediatric hematopoietic cell donors: ethical and clinical considerations. recommendations from a working group of the worldwide network for blood and marrow transplantation association. Biol Blood Marrow Transplant. 2016;22:96–103.
33. Behfar M, Faghihi-Kashani S, Hosseini AS, Ghavamzadeh A, Hamidieh AA. Long-term safety of short-term administration of filgrastim (rhG-CSF) and leukophresis procedure in healthy children: application of peripheral blood stem cell collection in pediatric donors. Biol Blood Marrow Transplant. 2018;24:866–70.
34. Pulsipher MA, Logan BR, Kiefer DM, Chitphakdithai P, Riches ML, Rizzo JD, et al. Higher risks of toxicity and incomplete recovery in 13- to 17-year-old females after marrow donation: RDSafe peds results. Biol Blood Marrow Transpl. 2019;25:955–64.
35. Switzer GE, Bruce J, Kiefer DM, Kobusingye H, Drexler R, Besser RM, et al. Health-related quality of life among pediatric hematopoietic stem cell donors. J Pediatrics. 2016;178:164–70.
36. Switzer GE, Bruce J, Kiefer DM, Kobusingye H, Drexler R, Besser RM, et al. Health-related quality of life among older related hematopoietic stem cell donors (>60 years) is equivalent to that of younger related donors (18 to 60 years): a related donor safety study. Biol Blood Marrow Transplant. 2017;23:165–71.
37. van Walraven SM, Straathof LM, Switzer GE, Lankester A, Korthof ET, Brand A, et al. Immediate and long-term somatic effects, and health-related quality of life of BM donation during early childhood. A single-center report in 210 pediatric donors. Bone Marrow Transpl. 2013;48:40–5.
38. Wiener L, Hoag JA, Pelletier W, Shah NN, Shaw BE, Pulsipher MA, et al. Transplant center practices for psychosocial assessment and management of pediatric hematopoietic stem cell donors. Bone Marrow Transplant. 2019;10:1.
39. Billen A, Madrigal JA, Shaw BE. A review of the haematopoietic stem cell donation experience: is there room for improvement? Bone Marrow Transpl. 2014;49:729–36.
40. Pulsipher MA, Brent LR, Kiefer DM, Chitphakdithai P, Riches ML, Rizzo JD, et al. Related peripheral blood stem cell donors experience more severe symptoms and less complete recovery at one year compared to unrelated donors. Haematologica. 2019;104:844–54.

AUTHOR CONTRIBUTIONS

SA, LI, AB, AH, BF performed donor assessments and contributed donor data. YCH, TG, SH, GN, JP, US, UZ performed RD FU and contributed FU data. IW, LZ administrate donor FU data at the registry. EB managed FU data and was liaison to ProMise. GN established/supervised FU at the registry and designed the study. GN, JMT reviewed the manuscript. JPH designed the study, performed statistical analysis and wrote the manuscript. MR analysed, interpreted data and wrote the manuscript. All authors contributed to data interpretation and the writing of the manuscript and approved the final version.

COMPETING INTERESTS

The authors declare no competing interests.

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