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Research Paper

Pre-transplantation Risks and Transplant-Techniques in Haematopoietic Stem Cell Transplantation for Acute Leukaemia

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ABSTRACT

Background: The role of conditioning intensity and stem cell source on modifying pre-transplantation risk in allogeneic haematopoietic stem cell transplantation (HSCT) is a matter of debate, but crucial when benchmarking centres.

Methods: This Retrospective, multicenter exploratory-validation analysis of 9103 patients, (55.5% male, median age 50 years; 1–75 years range) with an allogeneic HSCT between 2010 and 2016 from a matched sibling (N = 8641; 95%) or matched unrelated donor (N = 462; 5%) for acute myeloid (N = 6432; 71%) or acute lymphoblastic (N = 2671; 29%) leukaemia in first complete remission, and reported by 240 centres in 30 countries to the benchmark database of the European Society for Blood and Marrow Transplantation (EBMT) searched for factors associated with use of transplant techniques (standard N = 6375;70% or reduced intensity conditioning N = 2728;30%, respectively bone marrow N = 1945;21% or peripheral blood N = 7158;79% as stem cell source), and their impact on outcome.

Findings: Treatment groups differed significantly from baseline population ($p < 0.001$), and within groups regarding patient-, disease-, donor-, and centre-related pre-transplantation risk factors ($p < 0.001$); choice of technique did depend on pre-transplantation risk factors and centre ($p < 0.001$). Probability of overall survival at 5 years decreased systematically and significantly with increasing pre-transplantation risk score (score 2 vs 0/1 HR: 1·2, 95% c.i. [1·1–1·.3], $p = 0.002$; score 3 vs 0/1 HR: 1·5, 95% c.i. [1·3–1·7], $p < 0.001$; score 4/5/6 vs 0/1 HR: 1·9, 95% c.i. [1·6–2·2], $p < 0.001$) with no significant differences between treatment groups (likelihood ratio test on interaction: $p = 0.40$). Overall survival was significantly associated with selection steps and completeness of information ($p < 0.001$).

Interpretation: Patients' pre-transplantation risk factors determine survival, independent of transplant techniques. Transplant techniques should be regarded as centre policy, not stratification factor in benchmarking. Selection criteria and completeness of data bias outcome. Outcomes may be improved more effectively through better identifying pre-transplantation factors as opposed to refinement of transplant techniques.

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Research in context

Evidence before this study

To review previous evidence on the effect of conditioning and stem cell source on outcome, we searched PubMed for articles published in English using the MeSH terms "haematopoietic stem cell transplantation/HSCT" or "HCT" or "BMT" and "conditioning", respectively "reduced intensity conditioning", respectively "standard conditioning", respectively "stem cell source", respectively "peripheral blood", respectively "bone marrow". In addition, we searched for "HSCT/HCT/BMT" and "benchmarking". Studies confirmed that pre-transplantation risk factors, such as patient age, donor type, disease and disease stage correlate with overall survival but left open whether transplant techniques can alter this pre-transplantation risk. Several reports claimed "reduced intensity conditioning" specifically for "elderly and frail patients". Retro- and prospective studies, including two randomized controlled trials provided conflicting results. Better information is relevant for individual patients; it is relevant when benchmarking is used to assess centre specific outcome. It is unknown whether transplant techniques should be considered as centre policy or as stratification factor.

Added value of this study

This retrospective multicenter study in a homogeneous group of patients with a well-defined disease fills the gap in the evidence base concerning the role of transplant techniques on pre-transplantation risk. Type of technique is determined by patients' criteria *and* centres' choice. Probability of overall survival at 5 years decreased systematically and significantly with increasing pre-transplantation risk, regardless of standard- or reduced intensity conditioning, of bone marrow or peripheral blood as stem cell source. In addition, the study showed the major impact of any selection process and incomplete data on outcome.

Implications of all the available evidence

The results from this study indicate that transplant technique should be considered as centre policy, rather than stratification factor in benchmarking. It indicates that focus should shift from fine-tuning transplant techniques to better defining and reporting pre-transplantation risk factors.

1. Introduction

Allogeneic haematopoietic stem cell transplantation (HSCT) provides a curative treatment for selected patients with severe congenital or acquired disorders of the haematopoietic system, but remains associated with significant morbidity and mortality, despite improvements over the last decades [1–3]. Relapse of the primary disease or death due to early or late treatment complications are the main determinants of failure [4]. A wide range of patient-, donor-, disease-, and centre-related pre-, peri-, and post-transplantation risk factors contributes to final outcome [1,3,5].

A simple score of five pre-transplantation factors was established and validated 20 years ago to predict the risk for failure, and to permit an integrated risk-adapted approach [6,7]. Patient selection, disease classification, disease treatment, donor choice and transplant techniques have since changed [2–5,8,9]. New concepts including co-morbidity index or disease risk score have been developed to better predict outcome [10]. Pilot studies, based on carefully conducted animal studies, have suggested that novel transplant technologies might mitigate against the elevated mortality for high risk patients, and open up transplantation for "elderly and frail patients" [11–13]. Pro- and retrospective studies have yielded conflicting results [14–16].

The answer is relevant for individual patients but also when transplant centres are compared for their performance. Benchmarking is now advocated to improve patient outcome [17–20]. It is used in several countries, and has been incorporated as an accreditation standard since the 6th edition of the FACT-JACIE standards [21]. The best method is not defined. The potential risk, to focus more on ranking than patient perspectives, has only recently been outlined [22].

Within the framework of an ongoing JACIE/EBMT project, we were interested to learn more about the respective roles of transplant techniques and pre-transplantation risks on final outcome, and to find out about their respective place in benchmarking. We concentrated on conditioning intensity and stem cell source. Conditioning is required to reduce rejection and disease burden; stem cells are needed to restore hematopoiesis [1–3]. Both techniques present with a Janus-face [23]. Decreased conditioning intensity might reduce early mortality but increase risk of relapse; peripheral blood as stem cell source can lead to a more rapid engraftment, but to a higher rate of chronic graft-versus-host disease (GvHD) [24]. We focused on a well-defined, homogeneous, and recent patient cohort, with the most frequent indication for allogeneic HSCT, acute leukaemia [2,8,9]. We looked for factors associated with the choice of transplant techniques and we asked whether the effect of well-known pre-transplantation risk factors would be modified by the transplant techniques. We wanted to learn whether the latter should be used as adjustment criteria for benchmarking, or regarded as part of the centre's policy.

2. Methods

2.1. Study Design, Patient Selection and Final Patient Population

This retrospective observational analysis is an extract from the EBMT megafile (www.ebmt.org), locked at a specific time point, and kept unmodified for benchmarking questions without re-contacting centres. It holds information on 407,460 (196,175; 48% allogeneic) patients treated between 2010 and 2016 by an allogeneic HSCT for an acquired haematological malignancy, and reported by 240 teams in 30 countries (Table 1). They correspond to approximately 80% of patients with HSCT as listed in the EBMT activity survey within the same time frame [8]. We concentrated on patients (adult and paediatric) with a transplant from an HLA-identical sibling or HLA-matched unrelated bone marrow or peripheral blood stem cell donor for primary acute myeloid or lymphoblastic leukaemia in 1st complete remission (1st CR) (see Supplementary Table 1), and information on the key risk factors (see below) (Table 2) [11]. Patient survival data were updated as of January 1st, 2018. This final cohort included 6375 patients (70%) with standard, 2728 patients (30%) with reduced intensity conditioning, 1945 patients (21%) with bone marrow, 7158 (79%) with peripheral blood as stem cell source (Table 2). They represent about 10% of all allogeneic HSCT in this benchmark cohort.

2.2. Definitions

We defined acute leukaemia as primary, when "primary" was reported to the database with the main diagnosis at time of diagnosis *and* at time of transplant. The time intervals from diagnosis to 1stCR and from 1stCR to transplant were categorized into two groups each: ≤3 months versus >3 months [5].

Donor type was restricted to four categories depending on donor-recipient matching (matched sibling donors or matched unrelated donors only) and on donor and recipient sex: HLA-identical, HY^- or HY^+ sibling, and HLA-matched, HY^- or HY^+ unrelated donors. HY^+ refers to a female donor for a male recipient, HY^- to all other donor-recipient sex combinations [23].

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Table 1
Steps of the selection process of the 9103 study patients out of 407,460 patients with a haematopoietic stem cell transplant and reported to the EBMT benchmark file: selection criteria and comparisons of overall survival between selected and excluded patients.[a]

Steps	Exclusion criterion	N initial	N excl	N end	HR (95% CI)[b]	Comment
Start	Starting file			407,460	n.a.	
Step 1	Year transplant <2010	407,460	211,285	196,175	·94 (·93–·95)***	>2010 better
Step 2	Autologous HSCT	196,175	112,688	83,487	2·24 (2·20–2·28)***	Allogeneic HSCT worse
Step 3	Diagnosis not acute leukaemia	83,487	37,609	45,878	1·13 (1·.10–1·16)***	Acute leukaemia worse
Step 4	Cord blood as stem cell source	45,878	2042	43,836	·84 (·78–·90)***	Non-cord blood donors better
Step 5	Missing information[c]	43,836	4506	39,330	·88 (·83–·94)***	Patients with full information better
Step 6	Non-primary[d] acute leukaemia	39,330	3676	35,654	·76 (·72–·80)***	Primary acute leukaemia better
Step 7	Non 1st CR	35,654	13,239	22,415	·55 (·53–·56)***	1st CR better
Step 8	Donor not HLA-identical	22,415	13,233	9182	·84 (·81–·88)***	HLA-identical donor better
Step 9	Time Dx-Tx >12 months	9182	79	9103	·86 (·58–1·26)n.s.	No difference
Sub-group analysis	No information time Dx-1st CR and 1st CR-Tx	9103	6517	2586	·93 (·85–1·01)*	Patients with detailed information better

Dx-Tx: Time from diagnosis to transplant; Dx-1st CR: Time from diagnosis to 1st complete remission; 1st CR-Tx: Time from 1st complete remission to transplant.
[a] According to the STROBE checklist: (https://www.strobe-statement.org/index.php?id=available-checklists). For details of exclusions, and reasons to do so, see Methods section.
[b] Hazard ratios and 95% confidence intervals in overall survival of remaining versus excluded patient population.
[c] Full information includes details in the report regarding age, sex of patient and donor, main disease and stage of the disease, donor type, stem cell source, and type conditioning.
[d] For definition, see Methods; in addition, time interval from diagnosis to 1st CR (if known) had to be <6 months.
n.s p ≥ 0.1.
* p = 0.09.
*** p ≤ 0.0001.

Table 2
Characteristics of 9103 patients with a haematopoietic stem cell transplant for primary acute leukaemia (acute myeloid leukaemia or acute lymphoblastic leukaemia) in 1st complete remission between 2010 and 2016, depending on applied transplant technique.

		Applied transplant techniques: conditioning and source of stem cells									
		0 MAB + BM		1 MAB + PB		10 RIC + BM		11 RIC + PB		Total	
		Count	Column valid N %	Count	Column valid N %	Count	Column valid N %	Count	Column valid N %	Count	Column valid N %
Disease	Prim.AML	980	56·9%	3193	68·6%	175	78·1%	2084	83·2%	6432	70·7%
	Prim ALL	741	43·1%	1461	31·4%	49	21·9%	420	16·8%	2671	29·3%
Patient sex	Male	961	55·8%	2597	55·8%	116	51·8%	1378	55·0%	5052	55·5%
	Female	760	44·2%	2057	44·2%	108	48·2%	1126	45·0%	4051	44·5%
Patient age@trpl	<20 years	719	41·8%	358	7·7%	28	12·5%	15	0·6%	1120	12·3%
	20–40 years	496	28·8%	1822	39·1%	36	16·1%	170	6·8%	2524	27·7%
	40–60 years	454	26·4%	2198	47·2%	100	44·6%	1292	51·6%	4044	44·4%
	>60 years	52	3·0%	276	5·9%	60	26·8%	1027	41·0%	1415	15·5%
Karnofsky	≤80	284	16·5%	610	13·1%	40	17·9%	562	22·4%	1496	16·4%
	90,100	1437	83·5%	4044	86·9%	184	82·1%	1942	77·6%	7607	83·6%
Donor	Idsib, HY−	1249	72·6%	3330	71·6%	151	67·4%	1756	70·1%	6486	71·3%
	Idsib, HY+	400	23·2%	1110	23·9%	54	24·1%	591	23·6%	2155	23·7%
	MatchUnrel, HY−	63	3·7%	190	4·1%	17	7·6%	138	5·5%	408	4·5%
	MatchUnrel, HY+	9	0·5%	24	0·5%	2	0·9%	19	0·8%	54	0·6%
Accredited by 2012	No	944	54·9%	2947	63·3%	127	56·7%	965	38·5%	4983	54·7%
	Yes	777	45·1%	1707	36·7%	97	43·3%	1539	61·5%	4120	45·3%
Intvdiag-1stCR	0–3 months	623	91·9%	779	85·0%	54	83·1%	796	85·9%	2252	87·1%
	3–6 months	55	8·1%	137	15·0%	11	16·9%	131	14·1%	334	12·9%
Intv1stCR-trpl	0–3 months	339	50·0%	475	51·9%	27	41·5%	467	50·4%	1308	50·6%
	>3 months	339	50·0%	441	48·1%	38	58·5%	460	49·6%	1278	49·4%
Pre-score	0/1	999	58·0%	1511	32·5%	50	22·3%	131	5·2%	2691	29·6%
	2	455	26·4%	1979	42·5%	67	29·9%	764	30·5%	3265	35·9%
	3	222	12·9%	923	19·8%	65	29·0%	1010	40·3%	2220	24·4%
	4/5/6	45	2·6%	241	5·2%	42	18·8%	599	23·9%	927	10·2%
	Total	1721	100·0%	4654	100·0%	224	100·0%	2504	100·0%	9103	100·0%

• P-values for Chi-square tests: donor (p = 0·03); interval 1st CR-trpl (p = 0·42); patient gender (p = 0·63); all others (p < 0.001).
MAC: myeloablative conditioning; RIC: reduced-intensity conditioning. For definitions, see Methods.
BM: bone marrow; PB: peripheral blood.
Idsib: HLA-antigen matched sibling donor; MatchUnrel: HLA-antigen matched unrelated donor.
HY^+: HY-antigen barrier positive; female donor for a male recipient; HY^-: all other donor-recipient sex combinations.
Intv diag-1stCR: Time from diagnosis to achieving 1st complete remission.
Intv 1st CR-trpl: Time from 1st complete remission to transplant.
Prescore: see Methods section for explanation.

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Conditioning intensity was used as previously defined and classified by the reporting team into standard or reduced intensity conditioning [23]. Stem cell source was restricted to bone marrow or peripheral blood; patients with cord blood or combined sources were excluded (Table 1).

All types of graft-versus-host disease (GvHD) prophylaxis were included, but ignored as factors in the analysis. Type of prophylaxis varied from centre to centre, and there is no documented superior combination regarding overall survival than a calcineurin inhibitor with or without methotrexate [9].

2.3. Statistical Analysis

This complex analysis comprised a multi-step process. First, we compared at each selection step overall survival of the included versus excluded patients (Table 1). For the final group of 9103 patients, a stratified Cox model (stratification by conditioning) was used to investigate possible non-proportionality due to differently shaped curves corresponding to conditioning intensity as reported in the literature [14–16]. The qualitative interaction (i.e. "crossing curves") could be resolved by incorporating the significant and strong interaction between stem cell source (bone marrow versus peripheral blood), and conditioning (standard versus reduced intensity conditioning). The interaction term was then replaced by a 4-level factor of the four combinations. Conditioning and stem cell source served therefore as adjustment factors, without comparing directly the types of transplant techniques with each other. All inference on the other factors remained virtually the same and the replacement of the interaction term by a 4-level covariate did facilitate the clinical interpretation of the other hazard ratios.

We then searched for factors associated with use of transplant technique. The likelihood of patients to receive reduced intensity conditioning was estimated by a logistic regression model using calendar year, patient age, Karnofsky (adult)/Lansky (paediatric) performance score, disease and donor type. A second estimate was obtained by adding the centre identification itself and whether the time between diagnosis and 1st CR was indeed reported by the respective centre. The former was used to estimate the average likelihood for the study population of receiving a reduced intensity conditioning based on patient pre-transplantation characteristics. The latter incorporated centre characteristics, i.e. the willingness to perform a reduced intensity conditioning procedure, and the centres' quality of reporting. In a similar approach, we estimated the likelihood of receiving peripheral blood compared to bone marrow as stem cell source.

For factors associated with outcome, the main endpoint was the probability of overall survival up to 5 years in a Cox model [10]. We used a modified EBMT pre-transplantation risk score [5]. Patient age (<20 years, 20–40 years, 40–60 years, >60 years; 0–3 score points), donor type (matched sibling or matched unrelated; 0–1 score points), HY status (HY^- vs HY^+; 0–1 score points), and Karnofsky/Lansky score (>80 versus ≤80; 0–1 score points) contributed to the final score (score 0 to maximum 6) (Table 2). As macro- and micro-economic covariates at the centre level, we used the country specific Human Development Index (www.hdi.org) and accreditation status [25]. Calendar year was included as a continuous covariate.

The analyses were first performed for the 6432 patients with acute myeloid leukaemia. Having developed the survival model, we checked that the results were valid also for the 2671 patients with acute lymphoblastic leukaemia in 1st CR separately (data not shown). After checking that no significant interaction took place between the diseases and the other covariates (Supplementary Table 1), we finally analyzed the combined data set of 9103 patients, but adjusting for disease to increase the power of the estimates.

The analyses were performed in SPSS version 25.

2.4. Organizational and Ethical Aspects

EBMT teams are required to obtain patients' consent for data transfer to EBMT in accordance with appropriate internal approval for their transplant programs and European Data Protection Regulations (GDPR) if applicable (https://eugdpr.org/). Adherence to these requirements and accuracy of data reporting is regularly audited within the JACIE accreditation process. The data set was locked at time of transfer to the statistical office. On purpose, to reflect a benchmarking process at time x, no attempt was made nor could be made to retrieve missing data. According to the laws in the Netherlands and Switzerland, no ethics approval was mandated for this analysis with anonymized data.

3. Results

3.1. Selection Process

The benchmark file population was reduced in 9 steps from the initial 407,460 patients to the final 9103. This process showed a systematic and significant change in overall survival at 5 years at each step of the selection process, with one exception. Results confirmed the well-known roles of year of transplant, main donor type, main disease category, cord blood as stem cell source, primary versus secondary leukaemia, and remission status (all $p < 0.001$) (Table 1). As a novel finding, we identified a significantly worse overall survival for patients with missing information (HR: 0·88; 0·83–·94) ($p < 0.001$), and a significant correlation between missing information, accreditation status and the age of the patients. Patients with incomplete information were more likely to be reported from non-accredited centres ($p < 0.001$) and were younger ($p < 0.001$), with a higher proportion of paediatric patients in non-accredited (18·4%) than accredited centres (10·2%). However, the proportion of patients with incomplete information was 20% for paediatric patients in both, accredited and non-accredited centres; it was 11·2% for adult patients in non-accredited, 5·5% in accredited centres (Supplementary Table 2a).

Information on the degree of matching (matched or mismatched) was missing in a much higher proportion of unrelated donor than sibling donor transplants (Table 1; step 8), leading to an under representative proportion of unrelated HSCT of only 5%.

3.2. Patient Population

There were significant differences between patients with acute myeloid and acute lymphoblastic leukaemia, between patients with standard or reduced intensity conditioning, and between patients with or without a known time interval from diagnosis to 1st CR (Table 2). Patients with primary acute lymphoblastic leukaemia were more likely to be males (60·2% vs 53·5%; $p < 0.001$), were younger (59·6% <40 years old vs 31·9%; $p < 0.001$), had lower Karnofsky/Lansky scores (18·1% ≤80 vs 15·7%; $p = 0.005$), but lower pre-transplantation scores (76·4% score 0–2 vs 60·8%; test for trend 0 + 1 vs 2 vs 3 vs 4 + 5 + 6 = $p < 0.001$).

Patients with reduced intensity conditioning were more likely to have acute myeloid leukaemia, (83% vs 66%; $p < 0.001$), were older (39·8% >60 years old vs 5·1%; $p < 0.001$), showed a higher proportion with low performance score (22% ≤80 vs 14%; $p < 0.001$), were preferentially given peripheral blood as stem cell source (92% vs 73%; $p < 0.001$) and had a higher proportion of unrelated donor transplants (6·5% vs 4·5%; $p = 0.001$) (Table 2).

Patients with information on time sub-intervals (time from diagnosis to 1st CR *and* time from 1st CR to transplant; N = 2586) were more likely to be reported from accredited than non-accredited centres (42·0% vs 17·2%; $p < 0.001$), and to have a lower proportion of patients with a low pre-score of 0–2 (56·9% vs 68·8%; $p < 0.001$) (Supplementary Table 2b). Overall survival of patients with full information, in

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contrast, was not different. Hence, centres with missing information had a higher proportion of lower risk patients.

3.3. Factors Associated With Transplant Practice

The analysis showed no apparent consistency in the choice of conditioning regimen across transplant centres, even when patients showed the same pre-transplantation characteristics (Supplementary Fig. 1a). The same applied to the likelihood of receiving peripheral blood compared to bone marrow as stem cell source (Supplementary Fig. 1b). Age ($p < 0.001$), Karnofsky's score ($p = 0.001$), disease ($p < 0.001$) and centre (fixed factor, $p < 0.001$) were highly significant in a logistic regression model for choice of conditioning, while donor type ($p = 0.80$) and calendar year ($p = 0.12$) were not. For the choice of type of stem cells, calendar time ($p = 0.001$), age ($p < 0.001$), Karnofsky's score ($p = 0.01$), donor type ($p = 0.017$), conditioning ($p < 0.001$)

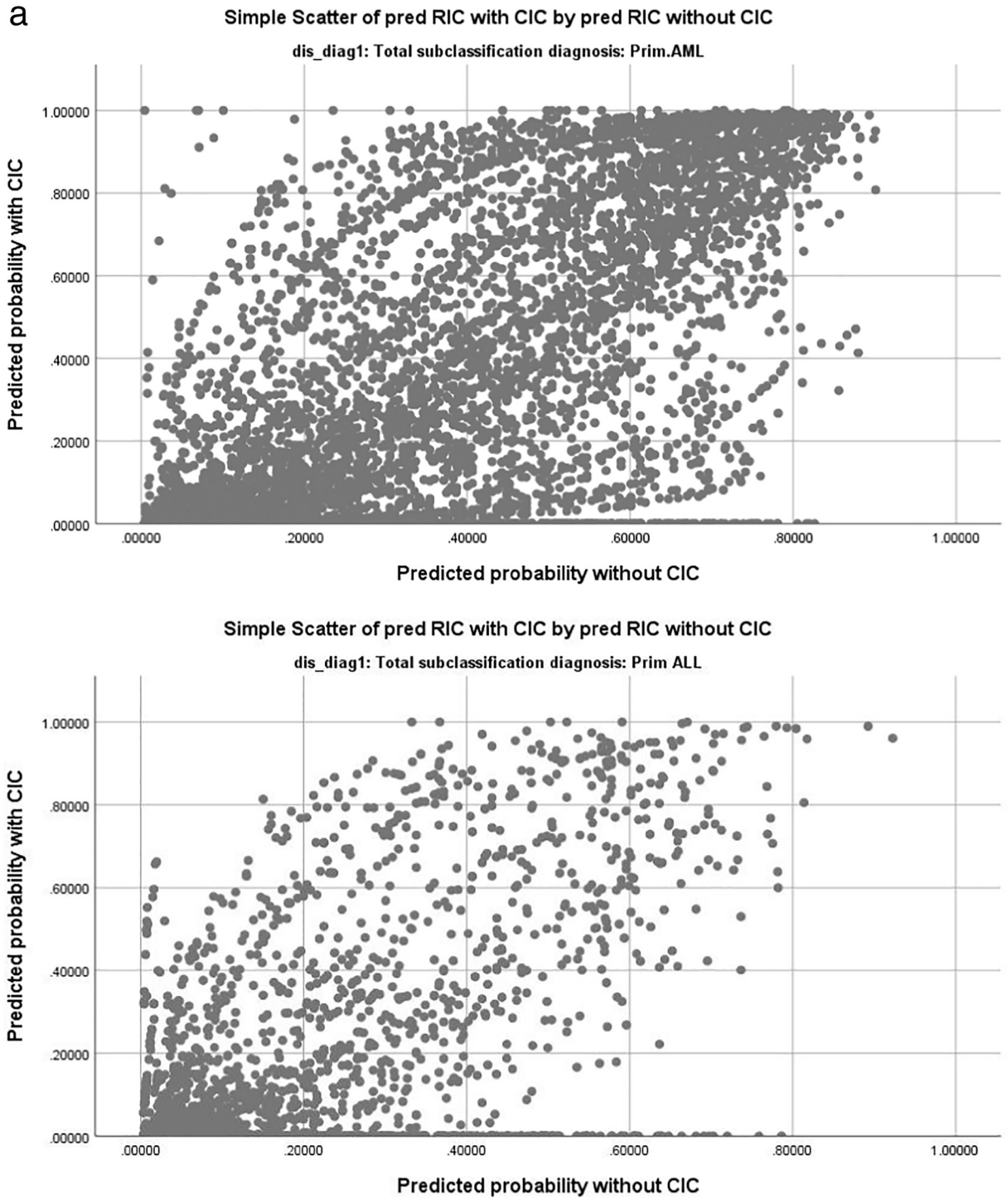

Fig. 1. Factors associated with choice of transplant technique for 9103 patients with a haematopoietic stem cell transplant for primary acute myeloid or acute lymphoblastic leukaemia in 1st complete remission. The graphs illustrate the probability of choice without (x-axis) and with (y-axis) considering transplant centre (CIC = Centre identification code of transplanting team) as factor. Each dot represents one patient. For details, see Methods section. a: Choice of reduced intensity conditioning (RIC). Top: AML (=acute myeloid leukaemia); Bottom: ALL (=acute lymphoblastic leukaemia). R-square: 0.51 (top) and 0.46 (bottom). b: Choice of peripheral blood as stem cell source, by patients' characteristics and conditioning. Top: AML; Bottom: ALL; Left: standard conditioning; Right: reduced intensity conditioning. R-square: 0.22 (top left), 0.13 (top right), 0.27 (bottom left), 0.24 (bottom right).

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b

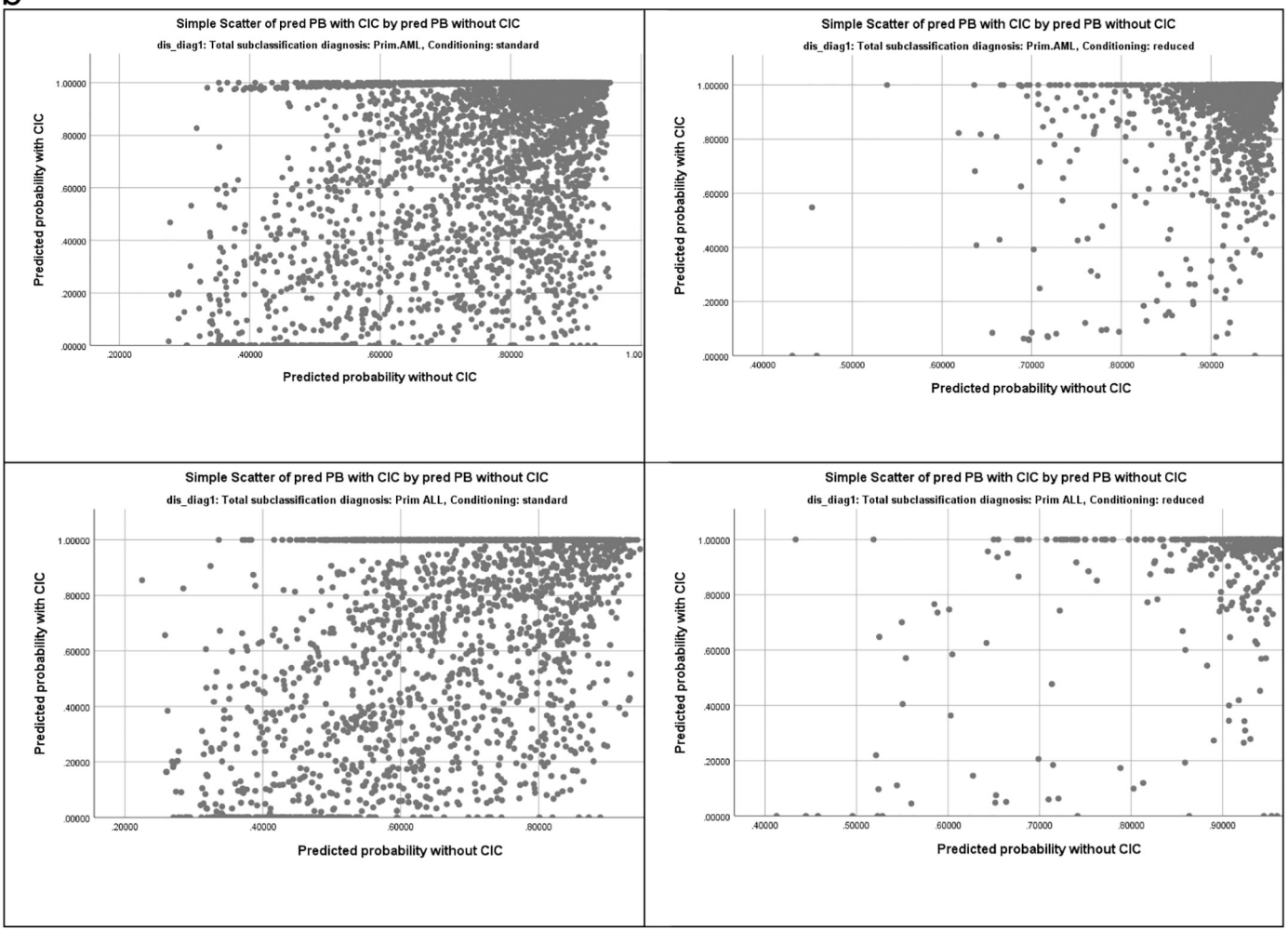

Fig. 1 (*continued*).

and centre (fixed factor, $p < 0.001$) were highly significant, while disease was not. The apparent arbitrariness, in terms of patient characteristics, to decide for or against a given transplant technology is reflected by the scattergram when the likelihood was calculated *with or without* centre identification code as a fixed factor in the model (Fig. 1a and b).

3.4. "Standard" Risk Factors and Univariate Outcome

Probability of overall survival at 5 years was 59% for patients with primary acute lymphoblastic leukaemia, 55% for patients with primary acute myeloid leukaemia (Fig. 2a). The survival pattern showed no indication for a 'Janus face' of conditioning intensity and stem cell source. Early overall survival at day 30 was 99% for the whole group. The analysis confirmed previously defined risk factors with a similar pattern for the four subgroups. Overall survival decreased systematically with increasing recipient age from 64% at 5 years for the <20 years old to 48% for the >60 years old patients ($p < 0.001$) (Supplementary Fig. 2a), and with increasing histoincompatibility ($p < 0.001$) (Supplementary Fig. 2b). Patients with a Karnofsky/Lansky score > 80 showed an overall survival of 58% at 5 years compared to 49% for those with a score of 80 or lower ($p < 0.001$) (Supplementary Fig. 2c). Combined in a score as summarized above, overall survival decreased stepwise from close to 80% at 5 years with score 0; 58% with score 2; 50% with score 3, to 45% with score 4 to less than 40% with scores 5and6 ($p < 0.001$) (Supplementary Fig. 2d).

3.5. Multivariate Effects of Pre-existing and Treatment-related Risk Factors on Outcome

Overall survival decreased in a risk adjusted Cox model systematically, significantly and stepwise with increasing pre-transplant risk score in a four group analysis: (score 2 vs 0/1 HR: 1·2, 95% c.i. [1·1–1·3], $p = 0.002$; score 3 vs 0/1 HR: 1·5, 95% c.i. [1·3–1·7], $p < 0.001$; score 4/5/6 vs 0/1 HR: 1·9, 95% c.i. [1·6–2·2], $p < 0.001$), whether source of stem cells and conditioning were included in the model together with their interaction or as stratification factors to allow for non-proportionality. There was no indication at all that conditioning or source would alter the inherent pre-transplantation risk (likelihood ratio test on interaction: $p = 0·40$) (Fig. 2b; Table 3).

The same effect was observed, with obvious loss of power, when the four groups of conditioning and stem cell source were analyzed independently. There was one exception in the small group of patients ($N = 224$) with reduced intensity conditioning and bone marrow as source (Supplementary Table 3).

The analysis was not designed to compare the four groups of conditioning and stem cell source. With all limitations, when acute myeloid leukaemia and acute lymphoblastic leukaemia patients were analyzed separately, the analysis showed no significant differences between the four groups for patients with acute myeloid leukaemia. It indicated significant differences for patients with acute lymphoblastic leukaemia, and best survival for patients with standard conditioning and bone marrow as source (Table 3).

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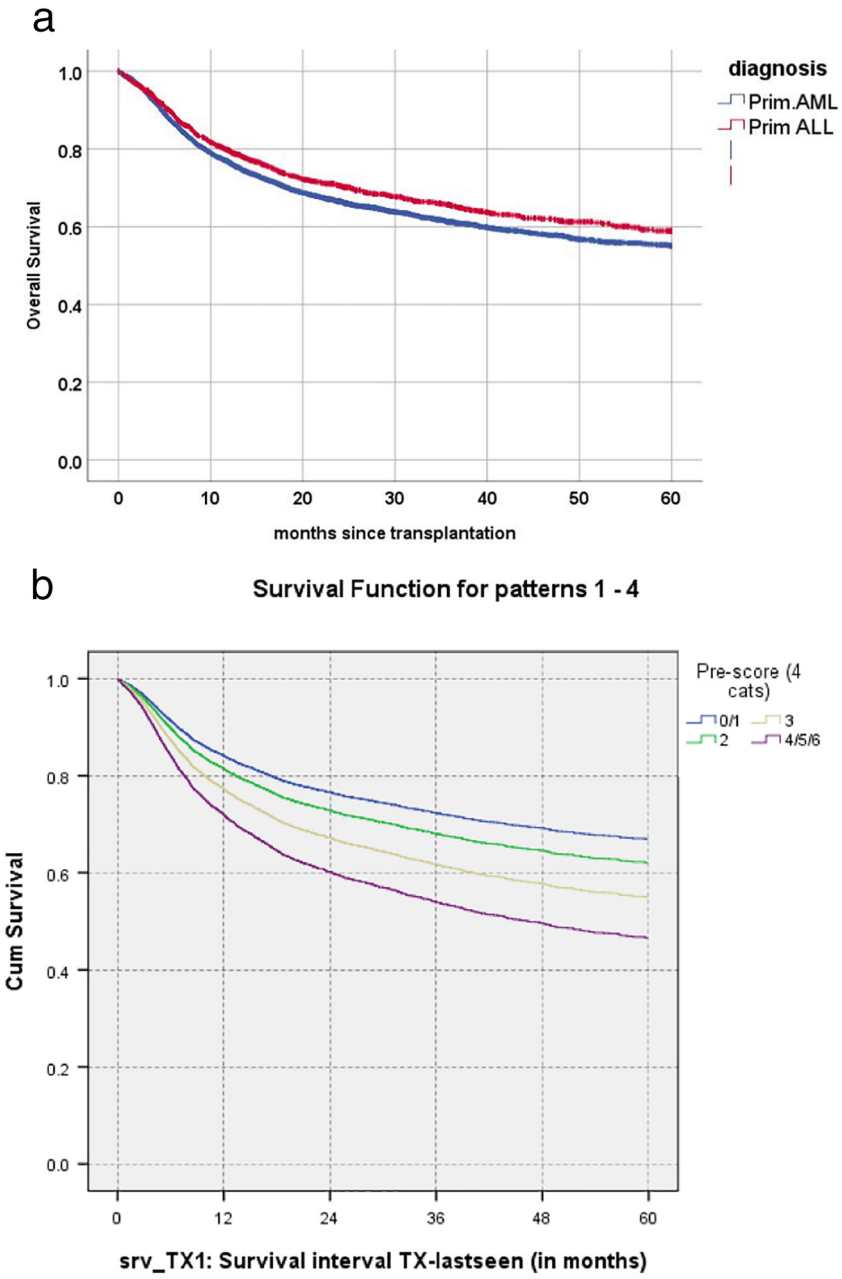

Fig. 2. Probability of overall survival of 9103 patients with a haematopoietic stem cell transplant for primary acute myeloid or acute lymphoblastic leukaemia in 1st complete remission during the years 2010 to 2016. a: Overall survival for the whole group, by main disease. AML = acute myeloid leukaemia; ALL = acute lymphoblastic leukaemia. b: Overall survival by pre-transplant-risk score. The curves represent probability of overall survival, as evaluated for a patient with a haematopoietic stem cell transplant for acute myeloid leukaemia in 1st complete remission in 2010, in an accredited centre in a country with the highest tertile for Human Development Index, using standard conditioning and peripheral blood as stem cell source. The survival curves are multivariately adjusted for accreditation, calendar year, Human Development Index, conditioning and source of stem cells. Pre-transplant scores are divided by scores 0/1, 2, 3, 4/5/6 (for details, see Methods section).

3.6. Additional Factors

The multivariate analysis confirmed a better overall survival in accredited centres (HR: ·886, 95% c.i. [·814–·965], p = 005), and a decrease of overall survival over calendar years time (HR: 1·031, 95% c.i. [1·007–1·055], p = 010, per year). It confirmed the lower probability of overall survival for patients with a longer time interval from diagnosis to 1st CR ($p < 0.001$), possibly reflecting the need for additional chemotherapy to achieve remission [5]. The effect was more pronounced in patients with acute lymphoblastic leukaemia (Supplementary Fig. 3). As previously described, the total time from diagnosis to transplant, not considering the subintervals, had no effect on outcome [5].

4. Discussion

This retrospective cohort analysis provided clear answers regarding both, factors associated with choice of transplant technique, and factors associated with outcome. As shown in this large homogeneous patient population, centre preference and pre-transplantation patients' characteristics determined the choice of transplant techniques, e.g. conditioning intensity and stem cell source. Pre-transplantation properties were predictive for overall survival. Overall survival at 5 years decreased systematically and stepwise from close to 80% to less than 40%, all in patients with acute leukaemia in 1st CR. No preferential type of conditioning changed this pattern or reduced mortality for patients with high

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Table 3
Factors associated with probability of overall survival. Data present the risk of mortality (Hazard ratios; HR, with 95% confidence intervals) for 9103 patients with a haematopoietic stem cell transplant for acute leukaemia (acute myeloid leukaemia:6432; acute lymphoblastic leukaemia:2671) in 1st complete remission, depending on pre-transplant risk factors (pre-score), centre's macro- and micro-economic factors, and choice of transplant technique. The model allowed for any interaction of the disease with the other risk factors.

	Sig.	HR	95.0% CI for Exp(B)	
			Lower	Upper
Pre-score (0/1)		1·0		
2	·002	1·187	1·063	1·326
3	·000	1·490	1·318	1·684
4/5/6	·000	1·902	1·634	2·215
Accredited by 2012	·005	·886	·814	·965
Percentile group of HDI (high vs other)	·380	1·041	·952	1·139
Year of treatment (per year)	·010	1·031	1·007	1·055
Evaluation for AML				
MAC + BM (ref cat)		1·0		
MAC + PB	·436	1·059	·917	1·221
RIC + BM	·978	1·004	·743	1·358
RIC + PB	·966	·997	·850	1·168
Evaluation for ALL:				
MAC + BM (ref cat)		1·0		
MAC + PB	·001	1·410	1·156	1·720
RIC + BM	·207	1·486	·803	2·748
RIC + PB	·000	1·775	1·389	2·270

• Adding interactions with disease was necessary to obtain a good proportional hazards model fit analyzing both diseases together (to increase the power for the estimates of the patient-related effects).
• All interactions between disease and the risk factors were non-significant except for the effect of conditioning and source of stem cells being modified by the disease ($p = 0.001$). The dose-response effect of the Pre-score may be assumed to be the same in AML and ALL.
• When estimating the same model separately among AML resp. ALL, the HR's were almost identical to the averaged effects in this table.
• **No** interpretation of the differing HR's for conditioning and source of stem cells between AML and ALL are attempted since the very definition of RIC could be different among AML and ALL and varying over calendar time and centres. Conditioning is merely used as a covariate to remove bias in the estimates of the pre-score and other patient related factors due to a possible correlation with conditioning and/or source of stem cells.
• MAC: myeloablative conditioning = reduced intensity conditioning; RIC: reduced-intensity conditioning. For definitions, see Methods.
Sig: p value; BM: bone marrow; PB: peripheral blood. HDI: Human Development Index.

pre-transplantation risk scores [13–16]. In addition, the study revealed a significant impact of the selection process, and a significantly worse overall survival for patients with incomplete information. These are novel findings, with direct consequences regarding benchmarking.

Benchmarking aims to improve the quality of patient care and outcomes [17–20]. Its success depends on widespread perception of 'fairness' through risk-adjustment for differences in patient population characteristics. Withholding known information, intentionally or not, can introduce bias. As shown in this study, completeness of information on known pre-transplantation risk factors appears to be essential for proper risk-adaptation. There is a scarcity of published information about variations between centres in quantity and quality of patient data reporting. The standards of the JACIE accreditation process aim to assure quality in this respect. Thus, the concept of 'fairness' becomes a mutual responsibility between a centre and the benchmarking system.

The analysis revealed additional novel elements. We found no signs of a 'Janus-face' effect of the transplant techniques [23]. The excellent day 100 survival precludes any early comparison. Regarding late survival, some patients with acute leukaemia in 1st complete remission are cured before the transplant, independent of conditioning [7]. Second, about one third of patients with matched donors never ever develop any graft-versus-host disease [26]. There is no tool yet available to identify such patients before the transplant.

Major caveats remain. There were significant differences between the groups which could not be adjusted for. We did not include methods of graft-versus-host disease prevention, or the "post-transplant cyclophosphamide" concept [8,9].

Information on "matching" of donor and recipient was too frequently missing, especially in unrelated donor transplants, leading to a too low number of unrelated HSCT compared to current practice [8,9]. This practice might reflect a general problem of the database. "Matched" as indicated by the reporting team, and used in the analysis, is still ill defined and might range from an 8/8 HLA-antigen to a 12/12 HLA-allelic match or beyond [9]. Transplant organizations are challenged to better define categories and to improve reporting.

Performance scores may fail to accommodate co-morbidities or the complex frailty of older patients [27]. Molecular, cytogenetic, and minimal residual disease status was not available, information which is especially relevant for individual decision-making [7]. Still, no attempt was made to retrieve additional data in order to reflect a status quo at any time of a benchmarking process. The large numbers and the consistency of the findings provide sufficient validity to the report.

The results provide guidance for future benchmarking strategies. Wide variations in infrastructure and use of transplant techniques are well described [4,8,9]; it may be challenging to incorporate the impact of these variations. Reassuringly and based on our results, transplant techniques should be considered a centre-specific ("policy") property rather than to be used as adjustment factor. In addition, "completeness of data reporting" almost becomes a surrogate marker for quality of transplant outcome.

In the current era of personalized medicine, HSCT has to provide a better outcome regarding overall survival, quality of life and costs. To achieve this goal, risks and benefits of HSCT have to be balanced continuously from diagnosis on with those of a non-transplant strategy [28]. Decisions should then be based on defined data, collected and analyzed according to the WHO principles [5,7,8,29].

Hence, assessing transplant centre quality through any accreditation or 'benchmarking' system should concentrate on completeness of data reporting, must define any selection beforehand, and must strive to include non-transplanted patients as well. The analysis also supports the hypothesis that transplant outcomes may be improved more effectively through identifying hitherto 'hidden' pre-transplantation factors as opposed to refinement of transplant techniques.

The implications of this report may apply to other disease categories as well, to other cellular treatment approaches, or when developing novel machine learning tools [30].

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Declaration of Competing Interest

RD, and JS initiated the study for the JACIE benchmarking project. AG and RB designed the study concept and drafted the manuscript. RB and HP conducted the statistical analysis. DN and JC were responsible for discussion of concept and critical reviewing of data. AvB, EMcG and HB were responsible for the data organization. JA, JC, HTG, MM, NK, AN, and DN were responsible for the data collection and data interpretation within their working parties and for advice. All authors have contributed to the writing, have seen the last version, and have approved of it. Writing of the manuscript was the sole responsibility of the authors. Dr. Gratwohl reports consulting fees from Takeda outside the submitted work. Dr. Duarte reports grants, personal fees and non-financial support from Merck Sharp and Dohme, personal fees and non-financial support from Cidara Therapeutics, personal fees and non-financial support from Omeros, personal fees and non-financial support from Jazz Pharmaceuticals, personal fees and non-financial support from Gilead Sciences, personal fees and non-financial support from MEDAC, personal fees and non-financial support from Therakos, personal fees and non-financial support from Incyte, outside the submitted work; Dr. Greinix reports personal fees from Therakos, Novartis, Cellgene, MSD, Sanofi, outside the submitted work. Dr. Mohty reports personal fees from Janssen, Celgene, Amgen, BMS, Sanofi, Jazz, Takeda, Adaptive Biotechnologies, and grants from Sanofi, Jannsen, Jazz, Roche, BMS outside the submitted work. Dr. Snowden reports personal fees from Janssen, Jazz, Kiadis, NHS ENGLAND, and MALLINCKRODT outside the submitted work. Dr. Niederwieser reports grants from Novartis, non-financial support from Amgen, other from Cellectis, other from Bayer, outside the submitted work; and support from the project “Zusammen gegen Krebs”. All other authors have no conflicts of interest to declare.

Appendix A. Supplementary Data

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