Outcomes of allogeneic haematopoietic stem cell transplantation from HLA-matched and alternative donors: a European Society for Blood and Marrow Transplantation registry retrospective analysis

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Summary

Background The introduction of donors other than HLA-matched siblings has been a pivotal change in stem cell transplantation. We aimed to assess the evolution of outcomes within donor groups over time and explore whether donor–recipient HLA disparity might be advantageous in patients with aggressive disease.

Methods In this retrospective, multicentre study, we assessed the outcomes for adult patients (≥18 years) with haematological malignancies who underwent their first allogeneic hematopoietic stem cell transplantation (HSCT) between Jan 3, 2001, and Dec 31, 2015, and were reported to the European Society for Blood and Marrow Transplantation. The donor types studied were matched sibling, matched unrelated, mismatched unrelated, haploidentical, and cord blood donors. Unrelated non-cord-blood donors and recipients were typed at the allelic level for *HLA-A*, *HLA-B*, *HLA-C*, and *HLA-DRB1*. We evaluated trends in overall survival, non-relapse mortality, relapse incidence, progression-free survival, acute and chronic graft-versus-host disease (GVHD), and GVHD-free and relapse-free survival following transplantation from various donor types (matched sibling, matched unrelated, mismatched unrelated, haploidentical, and umbilical cord blood), and compared transplantation outcomes across three epochs (epoch 1: 2001–05; epoch 2: 2006–10; and epoch 3: 2011–15). We used Kaplan-Meier estimators for survival probabilities and cumulative incidence functions accounting for competing risks for probabilities of GHVD, relapse, and non-relapse mortality, using multiple imputations by chained equations to deal with missing data. In epoch 3, we directly compared outcomes by donor group, stratified by a novel three-level disease-risk scheme.

Findings We included 106 188 patients in our analysis. The median follow-up was 4·1 years (IQR 1·7–7·7). Overall survival at 3 years increased with all donor groups between epochs 2 and 3 (matched sibling: 54·0% [95% CI 53·1–54·8] to 54·6% [53·6–55·6]; matched unrelated: 49·1% [48·0–50·2] to 51·6% [50·7–52·6]; mismatched unrelated: 37·4% [35·7–39·2] to 41·3% [39·5–43·1]; haploidentical: 34·5% [31·4–37·9] to 44·2% [42·1–46·3]; and cord blood 36·3% [33·9–39] to 43·7% [40·8–46·8]). Improvement in overall survival seems to be driven by a reduction in non-relapse mortality, except in cord blood HSCT recipients, who had a lower relapse incidence. Comparing donor groups across disease-risk strata using the novel disease-risk scheme, overall survival among recipients of matched sibling transplantations remained better than other donor groups except in high-risk disease, where overall survival with matched unrelated transplantations was not different.

Interpretation Overall survival following allogeneic stem cell transplantation is improving with substantial progress among recipients of haploidentical and cord blood HSCT. Nonetheless, the traditional donor hierarchy of matched sibling donors followed by matched unrelated donors and then other donors holds. Our findings warrant further investigation and could inform decision making and the development of donor-selection algorithms.

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See Comment page e545

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Introduction

Allogeneic haematopoietic stem cell transplantation (HSCT) is a curative treatment for haematological malignancies. Historically, HLA-matched sibling donors, available for only 30% of patients, have been the donors of choice. The establishment of unrelated-donor registries and introduction of unrelated umbilical cord blood donors and haploidentical related donors have resulted in donor availability for nearly all patients.[1] Traditionally, HLA-matched unrelated donors have been preferred in the absence of compatible matched sibling donors. Alternative donor groups such as HLA-mismatched

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Research in context

Evidence before this study

The rise of unrelated, haploidentical, and umbilical cord blood donors over the past two decades represents a pivotal change in the field of allogeneic haematopoietic stem cell transplantation (HSCT). We searched PubMed for the terms "allogeneic hematopoietic stem cell transplantation" and "trends" in reports published in any language from inception up to Oct 2, 2018, to identify relevant published clinical data. We identified 428 abstracts, 16 of which were retrospective analyses comparing outcomes over time in patients with haematological malignancies. The median number of patients included was 1106 (range 76–25 563). The majority of transplantations were done before 2005; four of the 16 studies included transplantations occurring after 2010. Indications for transplantation varied and grafts from matched sibling and matched unrelated donors predominated. Most studies showed a trend of improving overall survival over time in a cohort with heterogenous donor types, obscuring the relationship between donor and outcome.

Added value of this study

To our knowledge, this study presents the largest analysis of HSCT outcomes to date and provides an overview of the state of the field. We show that evolving practice in allogeneic HSCT has resulted in a narrowing gap between alternative (haploidentical and unrelated cord blood) and conventional (HLA-matched sibling and HLA-matched unrelated) donors. Nevertheless, in this comprehensive analysis, matched sibling donor transplantation is still associated with improved survival. Matched unrelated donors were only second to matched sibling donors, substantiating the importance of unrelated-donor registries. Because the proportion of patients relapsing have remained stable over time, future interventions should focus on strategies complementing the alloimmune effect of transplantation to achieve better disease control.

Implications of all the available evidence

The role of matched sibling donors has been challenged by some studies showing similar or even superior outcomes with other donor types. Our findings could be used to help to inform decision making and consent. Development of algorithms guiding the selection of donor, based on the probability of disease recurrence, can optimise the risk–benefit ratio in transplantation.

unrelated donors, HLA-haploidentical donors, and unrelated umbilical cord blood donors are considered tertiary options. Greater risk of graft-versus-host disease (GVHD) and non-relapse mortality with grafts from genetically distant donors drives the donor hierarchy.[2] However, such disparity might also provoke an alloimmune effect against the tumour.[3,4]

Transplantation techniques have evolved over the past two decades. Reduced-intensity conditioning regimens permit transplantation of older patients with high comorbidity burden.[5–7] Furthermore, matched unrelated donors have surpassed matched sibling donors as the leading source of stem cell grafts,[8] and the traditional donor hierarchy has been challenged.[9–11] Despite these changes, the underlying diagnosis and disease status at the time of transplantation remain principal determinants of outcome.[12]

We hypothesised that the effect of genetic disparity between donor and recipient on overall survival and non-relapse mortality has been attenuated over time. Furthermore, we sought to investigate whether such disparity might be advantageous in patients with aggressive disease.

Methods

Study design and participants

The European Society for Blood and Marrow Transplantation (EBMT) maintains a routinely audited registry of HSCT conducted by member institutions. Anonymised data are submitted by participating centres following patient informed consent. The EBMT scientific council approved this study in accordance with the Declaration of Helsinki.

We included adult patients (aged ≥18 years) with haematological malignancies who underwent their first allogeneic transplantation between Jan 3, 2001, and Dec 31, 2015, using stem cells derived from bone marrow, peripheral blood, or umbilical cord blood. Cases missing information on overall survival, the relationship between donor and recipient (related *vs* unrelated), diagnosis, or disease status were excluded.

Procedures

Unrelated non-cord-blood donors and recipients were typed at the allelic level for *HLA-A*, *HLA-B*, *HLA-C*, and *HLA-DRB1*. Donors mismatched at any of these alleles were defined as mismatched unrelated donors. Matching status of unrelated donors with only antigenic-level data was considered missing unless antigenic mismatch was documented, in which case the donor was classified as mismatched unrelated. The donor types studied were matched sibling (geno-identical sibling with matched *HLA-A*, *HLA-B*, and *HLA-DRB1* at the antigenic or allelic level), matched unrelated (unrelated donor matched at *HLA-A*, *HLA-B*, *HLA-C*, and *HLA-DRB1* at the allelic level), mismatched unrelated (unrelated donor with one or more mismatch at *HLA-A*, *HLA-B*, *HLA-C*, or *HLA-DRB1* at the allelic or antigenic level), haploidentical (sibling or other relative with two or more mismatches at *HLA-A*, *HLA-B*, or *HLA-DRB1* at the antigenic or allelic

level), and cord blood (unrelated donor umbilical cord blood; appendix p 14).

Conditioning-regimen intensity was categorised per the EBMT working definitions.[13] Broadly, conditioning regimens were considered myeloablative if stem cell support is mandatory due to irreversible cytopenia, whereas all other regimens were considered reduced intensity.

We analysed the following outcomes: overall survival (time from transplantation until death from any cause), non-relapse mortality (time from transplantation until death from any cause, with relapse as a competing event), relapse incidence (time from transplantation until relapse of the primary indication for transplantation, with non-relapse mortality as a competing event), progression-free survival (time from transplantation until relapse or death from any cause), and GVHD-free, relapse-free survival (time from transplantation until relapse, death, severe acute GVHD [grades 3–4] or extensive chronic GVHD).

Acute GVHD and severe acute GVHD were censored at 1 year and graded according to the modified Glucksberg criteria.[14] Acute GVHD was defined as the time to acute GVHD grade 2 or higher, and severe acute GVHD as the time to acute GVHD grade 3 or 4. Extensive chronic GVHD was graded according to the revised Seattle criteria[15] and defined as the time to extensive chronic GVHD. Relapse or non-relapse mortality were considered competing events for all GVHD assessments. Other outcome definitions are in the appendix (p 15). Follow-up data were collected until Aug 30, 2017.

To compare donor types, stratified by disease risk, we developed a disease-risk classification scheme, which was based on the risk for overall mortality associated with diagnosis–disease status combinations at transplantation. Diagnosis–disease status combinations were studied in a multivariable Cox model for overall survival. Three risk levels were defined: low risk (hazard ratio [HR] <1·33), intermediate risk (1·33≤HR<2·0), and high risk (HR ≥2·0), which correspond to a 50% increase in risk between the cutoffs. The classification scheme was developed in the first two epochs and validated on the third (appendix p 3).

Statistical analysis

We compared transplantation outcomes across three epochs: 2001–05 (epoch 1), 2006–10 (epoch 2), and 2011–15 (epoch 3). The probabilities of overall survival, progression-free survival, and GVHD-free, relapse-free survival were calculated using Kaplan-Meier estimators. Acute GVHD, chronic GVHD, non-relapse mortality, and relapse probabilities were estimated by cumulative incidence functions accounting for competing risks. To compare outcomes across epochs within each donor category, we used inverse probability weighting, adjusting for age, sex, diagnosis, time from diagnosis to transplantation, and disease status (appendix p 3). Since cord blood was considered a donor class, we did not adjust for graft source to avoid introducing collinearity into the model. Weighted Kaplan-Meier plots for overall survival were constructed for the entire population and within each donor group.

We analysed the influence of donor type in each disease-risk stratum (low, intermediate, or high, as previously defined) using a Cox regression adjusted for patient age, recipient and donor cytomegalovirus serostatus, female donor to male recipient status, time from diagnosis to transplantation, and conditioning intensity, with centre as a random effect. This analysis was restricted to epoch 3 to reflect contemporary practice.

Practices of HLA typing and the collection of these data have changed over the period studied. Excluding patients with missing information, categorising missing data as a separate category, or simple imputation using median or mode introduce bias into the analysis and compromise the generalisability and validity of results.[16] To mitigate these biases, we did multiple imputations by chained equations to take into account patients with missing values. Multiple imputations account for uncertainty associated with missingness and are considered the standard method for handling missing data. Multiple datasets are constructed imputing plausible values in place of missing ones. Regression analyses are done on each set and the results are pooled to obtain a robust estimation approximating the true effect.[16] Imputed datasets were generated separately for each donor type (sibling, unrelated, haploidentical, and cord blood) because of features unique to individual donors. Imputations were based on a range of variables related to patient, disease, donor, transplantation techniques, and outcomes, which might relate to missingness.

To assess the effect of missing HLA data in unrelated donors on our results, we did a series of sensitivity analyses in which missing data are studied under various assumptions (see appendix p 5). When the sensitivity

See Online for appendix

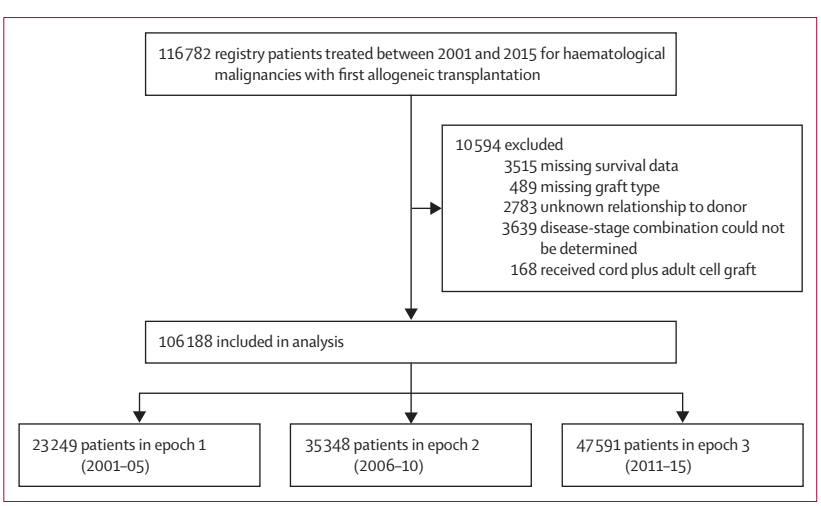


Figure 1: **Flow diagram**

	Epoch 1 (2001–05)	Epoch 2 (2006–10)	Epoch 3 (2011–15)	Missing data
Number of patients (percentage of total cohort)	23 249 (21·9%)	35 348 (33·3%)	47 591 (44·8%)	..
Age, years	44·2 (33·6–53·3)	48·5 (36·5–57·6)	51·9 (39·8–60·3)	0
Diagnosis	..	..	..	0
Acute leukaemia	11 670 (50·2%)	20 432 (57·8%)	27 490 (57·8%)	..
Myeloproliferative neoplasia*	3956 (17·0%)	3504 (9·9%)	4530 (9·5%)	..
Myelodysplastic syndrome	1725 (7·4%)	2821 (8·0%)	4986 (10·5%)	..
Indolent non-Hodgkin lymphoma	2005 (8·6%)	3230 (9·1%)	3431 (7·2%)	..
Plasma cell dyscrasia	2298 (9·9%)	2470 (7·0%)	2828 (5·9%)	..
Aggressive non-Hodgkin lymphoma	881 (3·8%)	1663 (4·7%)	2724 (5·7%)	..
Hodgkin lymphoma	714 (3·1%)	1228 (3·5%)	1602 (3·4%)	..
Disease risk†	..	..	..	0
Low	12298 (52·9%)	18 309 (51·8%)	25 326 (53·2%)	..
Intermediate	6146 (26·4%)	10 255 (29·0%)	14 605 (30·7%)	..
High	4805 (20·7%)	6784 (19·2%)	7660 (16·1%)	..
Donor type‡	..	..	..	0
Matched sibling	13 826 (59·5%)	15 575 (44·1%)	16 362 (34·4%)	..
Matched unrelated	758 (3·3%)	8693 (24·6%)	15 556 (32·7%)	..
Mismatched unrelated	533 (2·3%)	3123 (8·8%)	4089 (8·6%)	..
Unrelated (HLA unknown)	7550 (32·5%)	5528 (15·6%)	7248 (15·2%)	..
Haploidentical	278 (1·2%)	915 (2·6%)	3009 (6·3%)	..
Cord blood	304 (1·3%)	1514 (4·3%)	1327 (2·8%)	..
Cell source	..	..	..	0
Peripheral blood	17 140 (73·7%)	28 821 (81·5%)	40 340 (84·8%)	..
Bone marrow	5663 (24·4%)	4717 (13·3%)	5697 (12·0%)	..
Peripheral blood and bone marrow	142 (0·6%)	296 (0·8%)	227 (0·5%)	..
Cord blood	304 (1·3%)	1514 (4·3%)	1327 (2·8%)	..
Single unit	266/304 (87·5%)	814/1514 (53·8%)	556/1327 (41·9%)	..
Double unit	38/304 (12·5%)	700/1514 (46·2%)	771/1514 (58·1%)	..
Female-to-male transplantation	4979 (21·4%)	7157 (20·2%)	9039 (19·0%)	1771 (1·7%)
Conditioning	..	..	..	1314 (1·2%)
Myeloablative	13 824 (59·5%)	18 467 (52·2%)	23 395 (49·2%)	..
Reduced intensity	8707 (37·5%)	16 605 (47·0%)	23 876 (50·2%)	..
GVHD prophylaxis	..	..	..	16 612 (15·6%)
Methotrexate based	7508 (32·3%)	14 432 (40·8%)	19 934 (41·9%)	..
Mycophenolate mofetil based	2367 (10·2%)	10 120 (28·6%)	17 319 (36·4%)	..
Other	3253 (14·0%)	6012 (17·0%)	8631 (18·1%)	..
Haploidentical donor T-cell management§	..	..	..	453/4202 (10·5%)
Ex-vivo T-depletion	27/249 (10·8%)	125/802 (15·6%)	70/2698 (2·6%)	..
Post-transplant cyclophosphamide based	1/249 (0·4%)	71/802 (8·9%)	2050/2698 (76·0%)	..
Anti-thymocyte globulin based	221/249 (88·8%)	606/802 (75·6%)	578/2698 (21·4%)	..
Cytomegalovirus serotype	..	..	..	18 602 (17·5%)
Donor negative, recipient negative	3512 (15·1%)	7604 (21·5%)	11 538 (24·2%)	..
Donor negative, recipient positive	2577 (11·1%)	6919 (19·6%)	10 082 (21·2%)	..
Donor positive, recipient negative	1456 (6·3%)	3093 (8·8%)	4176 (8·8%)	..
Donor positive, recipient positive	4838 (20·8%)	12 477 (35·3%)	19 314 (40·6%)	..

Data are n (%) or median (IQR). Number of transplantations done by country is presented in the appendix (p 27). GVHD=graft-versus-host disease. *Includes patients with concomitant myelodysplastic syndrome or overlap of myelodysplastic syndrome and myeloproliferative neoplasm. †A three-level disease risk scheme that was developed on epochs 1 and 2 and validated on epoch 3 (see Methods). ‡Relationship between donor and recipient (related *vs* unrelated) is known in all cases. Missing cases represent only unknown HLA-match status for unrelated donors and are designated in a separate category. §Patients who received both anti-thymocyte globulin and post-transplant cyclophosphamide were considered to have received post-transplant cyclophosphamide-based therapy.

Table 1: **Population characteristics**

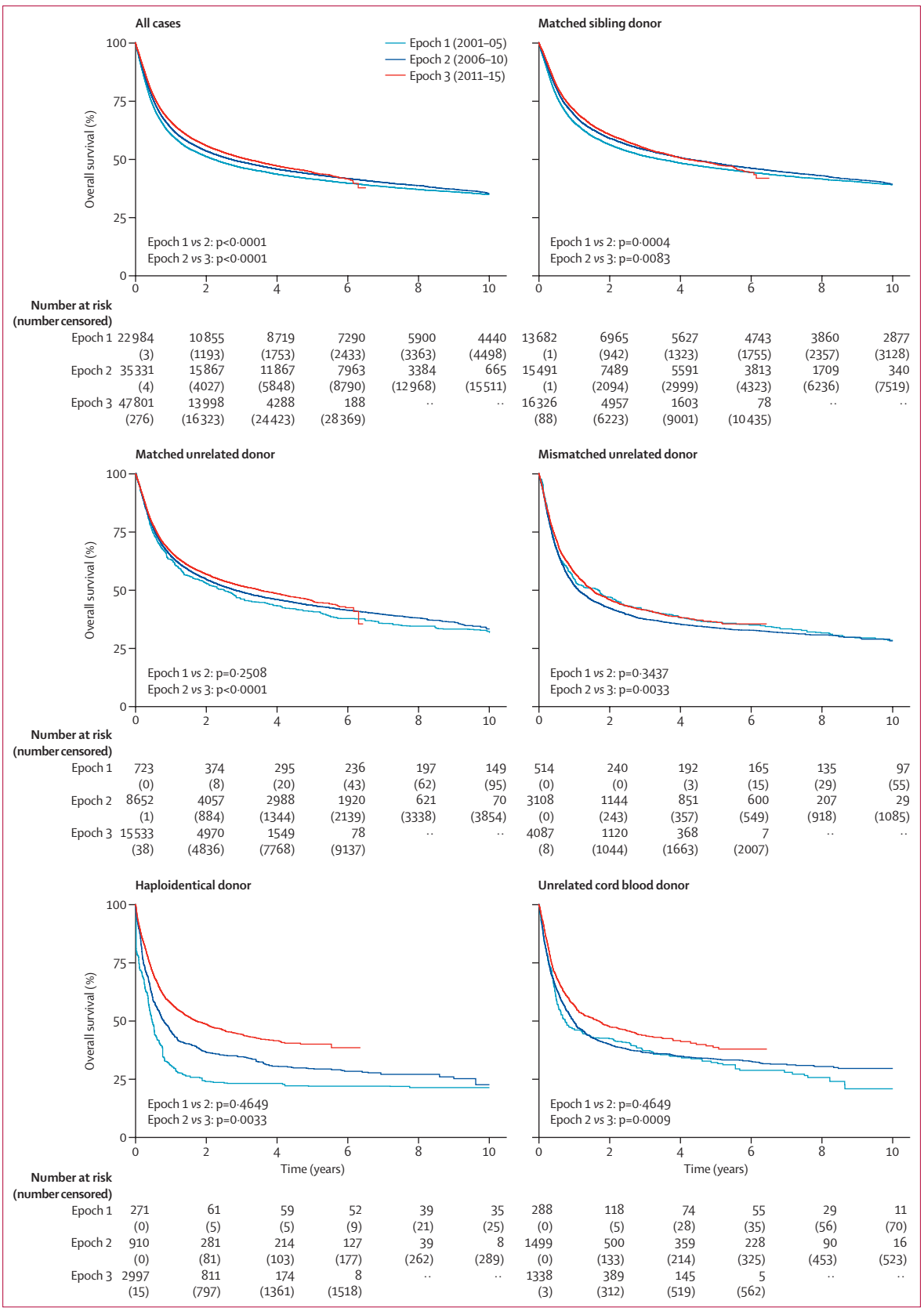


Figure 2: **Kaplan-Meier plots for overall survival by donor and epoch**
Kaplan-Meier plots are adjusted by inverse probability weighting to account for changing population characteristics over time. In epoch 3, follow-up at the 8-year and 10-year timepoints was not available. Unweighted results are presented in the appendix (p 28).

	Cases	Estimate (95% CI)			FDR-adjusted Cox p value	
		Epoch 1 (2001–05)	Epoch 2 (2006–10)	Epoch 3 (2011–15)	Epoch 1 *vs* 2	Epoch 2 *vs* 3
3-year overall survival	106 188	46·3% (45·6–47·0)	48·7% (48·2–49·3)	50·5% (49·9–51·0)	<0·0001	<0·0001
Matched sibling	45 489	51·2% (50·4–52·1)	54·0% (53·1–54·8)	54·6% (53·6–55·6)	0·0005	0·0083
Matched unrelated	24 939	46·0% (42·5–49·8)	49·1% (48·0–50·2)	51·6% (50·7–52·6)	0·25	<0·0001
Mismatched unrelated	7722	41·4% (37·3–45·9)	37·4% (35·7–39·2)	41·3% (39·5–43·1)	0·34	0·0033
Haploidentical	4174	23·0% (18·5–28·7)	34·5% (31·4–37·9)	44·2% (42·1–46·3)	0·46	0·0033
Cord blood	3130	37·1% (31·9–43·2)	36·3% (33·9–39)	43·7% (40·8–46·8)	0·46	0·0086
3-year non-relapse mortality	105 332	27·2% (26·5–27·8)	25·3% (24·9–25·8)	23·5% (23·1–24·0)	<0·0001	<0·0001
Matched sibling	45 094	22·6% (21·9–23·4)	19·8% (19·2–20·5)	18·1% (17·4–18·8)	<0·0001	<0·0001
Matched unrelated	24 825	24·4% (20·4–28·2)	26·3% (25·3–27·3)	24·8% (24·1–25·6)	0·081	<0·0001
Mismatched unrelated	7685	31·3% (26·2–36·0)	36·6% (34·8–38·3)	33·4% (31·7–35·0)	0·82	0·028
Haploidentical	4142	59·3% (42·4–71·2)	39·8% (36·1–43·3)	27·3% (25·5–29·0)	0·12	0·0033
Cord blood	3105	38·4% (31·4–44·7)	34·1% (31·5–36·5)	33·0% (30·1–35·8)	0·16	0·15
3-year relapse incidence	105 332	34·0% (33·3–34·7)	33·6% (33·1–34·2)	34·1% (33·6–34·6)	0·045	0·46
Matched sibling	45 094	34·5% (33·6–35·3)	35·6% (34·8–36·4)	36·8% (35·9–37·8)	0·47	0·44
Matched unrelated	24 825	37·1% (32·5–41·4)	31·8% (30·7–32·8)	31·0% (30·1–31·8)	0·45	0·36
Mismatched unrelated	7685	35·8% (30·2–40·9)	30·6% (28·9–32·3)	32·4% (30·7–34·0)	0·069	0·33
Haploidentical	4142	21·8% (12·3–30·2)	31·6% (28·0–35·0)	33·2% (31·3–35·1)	0·051	0·87
Cord blood	3105	30·8% (23·8–37·2)	34·7% (32·2–37·2)	28·7% (25·8–31·6)	0·85	0·0001
3-year progression-free survival	105 332	38·8% (38·2–39·5)	41·0% (40·5–41·6)	42·4% (41·8–42·9)	<0·0001	<0·0001
Matched sibling	45 094	42·9% (42·0–43·8)	44·6% (43·8–45·4)	45·0% (44·1–46·0)	0·054	0·10
Matched unrelated	24 825	38·4% (35·0–42·2)	41·9% (40·9–43·0)	44·2% (43·3–45·1)	0·22	<0·0001
Mismatched unrelated	7685	32·9% (29·1–37·3)	32·8% (31·2–34·6)	34·3% (32·6–36·0)	0·24	0·023
Haploidentical	4142	19·0% (14·8–24·3)	28·6% (25·7–31·9)	39·5% (37·5–41·5)	0·82	0·055
Cord blood	3105	30·7% (25·8–36·6)	31·2% (28·8–33·8)	38·2% (35·4–41·3)	0·44	0·0001

Table shows adjusted outcomes over time, with outcomes adjusted using inverse probability weighting (appendix p 3). Additional comparisons (acute and chronic GVHD and GVHD-free, relapse-free survival) are shown in the appendix (p 16); adjustment for multiple testing includes both sets of comparisons. FDR=false-discovery rate. GVHD=graft-versus-host disease.

Table 2: **Outcomes by epoch and donor type**

analyses resemble the primary analysis under reasonable assumptions, the imputed results are considered to be robust.

All p values are two sided and values less than 0·05 were considered statistically significant. Correction for multiple comparisons was done with the Benjamini-Hochberg procedure (false-discovery rate <5%) for comparison of characteristics or outcomes over time. All other analyses were considered hypothesis generating and no adjustment was done.

Data processing was achieved using SPSS (version 25.0). Analyses were done in R (version 3.4.3) using the packages survival (version 2.44–1.1), cmprsk (version 2.2–7), mice (version 2.25), prodlim (version 2018.04.18), survey (version 3.35–1), and shiny (version 1.3.2).

Role of the funding source

The funders had no role in the study design, data collection and analysis, or writing the report. The first three authors and the corresponding author had full access to all data. All authors shared the responsibility for the final decision to submit the report for publication.

For the **interactive visualisation** see https://joshuafein.shinyapps.io/table1supp

Results

Of the 116 782 registry patients treated between 2001 and 2015, 106 188 were included in the analysis (figure 1). Completeness of follow-up at 3 years post transplantation was 76·0% (160 236·2 person-years out 210 934·6 possible person-years of follow-up).[17] Median follow-up for surviving patients was 4·1 years (IQR 1·7–7·7). The number of allogeneic HSCTs, the median age of recipients, and use of reduced-intensity conditioning regimens have all increased over time (table 1; appendix p 6). Acute leukaemia remains the leading indication for HSCT. The proportion of transplantations from unrelated donors has consistently increased, with a concomitant reduction in mismatched sibling donor transplantations. Most unrelated donors have an 8/8 HLA match with the recipient. Haploidentical donors are also increasingly used, representing 6·3% of transplants between 2011 and 2015 (table 1). Interactive visualisation of population characteristics by diagnosis is available online.

Overall survival at 3 years post transplantation steadily increased across all epochs in the complete cohort and for recipients of matched sibling HSCT, and between

epochs 2 and 3 in recipients of matched unrelated HSCT (figure 2; table 2). Overall survival also improved between epochs 2 and 3 for haploidentical and cord blood transplantations. Non-relapse mortality declined in the last epoch, most notably for recipients of haploidentical transplantations and, to a lesser extent, for those of matched sibling, matched unrelated, and mismatched unrelated transplantations (table 2). Although non-relapse mortality remained similar for cord blood HSCT recipients, a reduction in relapse incidence was observed between epochs 2 and 3 (table 2). This was consistent in single-unit and double-unit cord blood transplantation (appendix p 17). Proportions of patients experiencing relapse did not differ over time for the other donor groups. Among cord blood HSCT recipients, the probability of progression-free survival was 31·2% (95% CI 28·8–33·8) in epoch 2 and 38·2% (35·4–41·3) in epoch 3 (p<0·0001); in haploidentical transplantations, progression-free survival was 28·6% (25·7–31·9) in epoch 2 and 39·5% (37·5–41·5) in epoch 3 (p=0·055; table 2).

Severe acute GVHD (grade 3–4) declined slightly among matched sibling HSCT recipients between the first two epochs (9·7% [95% CI 9·2–10·3] to 8·4% [7·9–8·8]; p=0·0002; appendix p 16). An increase in severe acute GVHD was observed among cord blood HSCT recipients between epochs 2 and 3 (11·1% [9·4–12·8] to 14·8% [12·7–16·8]; p=0·046). A modest reduction in extensive chronic GVHD contributed to the overall rise in GVHD-free, relapse-free survival, a measure reflecting freedom from morbidity and mortality after transplantation.[18] Overall, GVHD-free, relapse-free survival improved with all donor types in the last epoch, ranging from 24·3% (22·7–25·9) with mismatched unrelated transplantation to 33·2% (31·3–35·2) with haploidentical transplantation (appendix p 16).

Because outcomes were analysed using only complete cases, we did a sensitivity analysis imputing HLA-match status in unrelated donors. Results were broadly consistent in the comparison between epochs 2 and 3 (appendix p 7, 18). Among unrelated donors, 38·3% (20 326 of 53 078) did not have high-resolution typing reported, with the highest proportion of missingness in the first epoch; this higher proportion of missingness accounts for more variation between epochs 1 and 2, where a statistically significant improvement in overall survival, non-relapse mortality, and progression-free survival was observed in imputed cases among recipients of mismatched unrelated transplantations but not in the complete cases (appendix p 18). Lower rates of missing data were observed in additional variables.

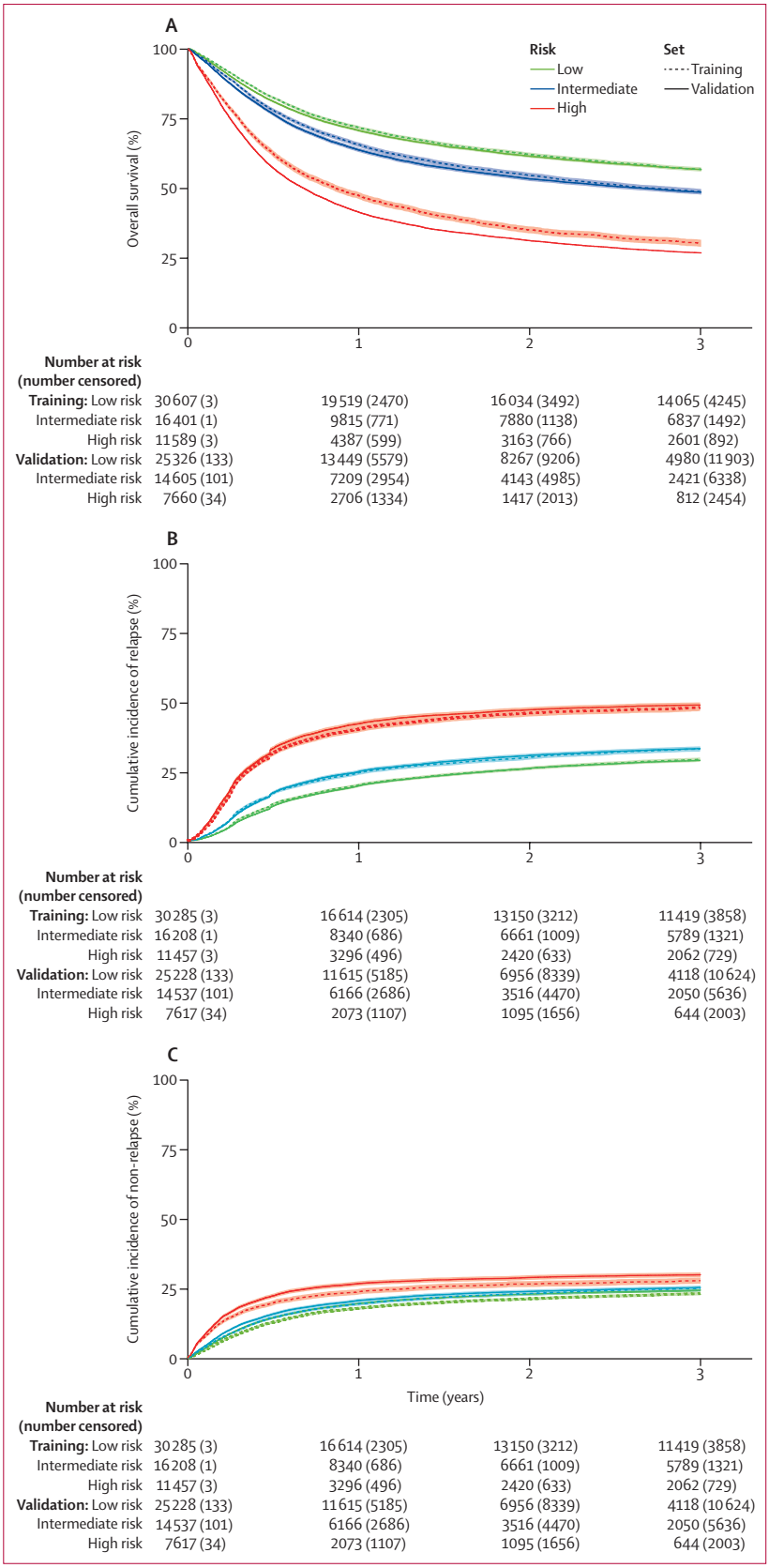
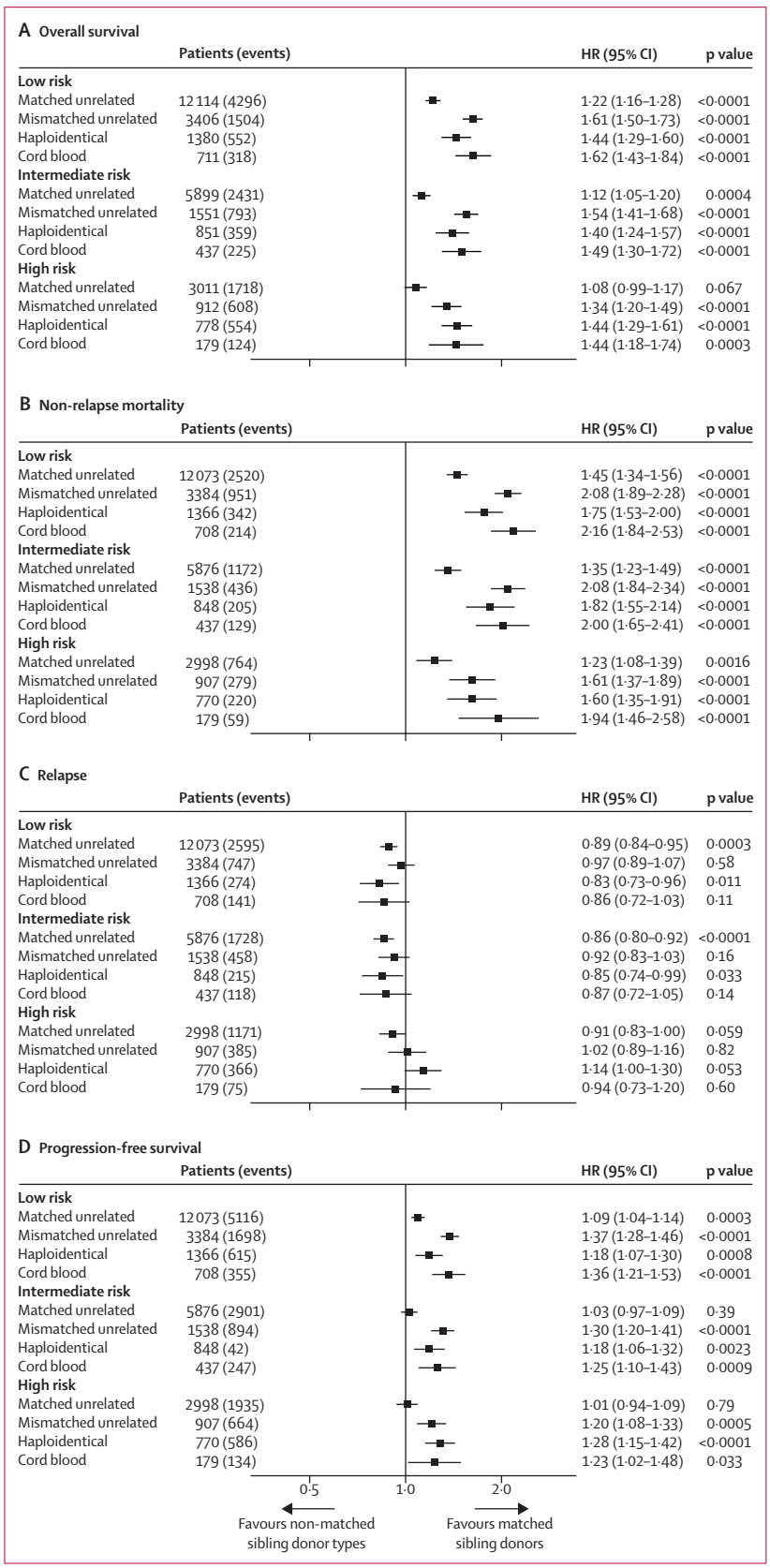


Figure 3: **EBMT disease-risk stratification scheme**
Performance of the three-level disease-risk stratification scheme on the training (epochs 1 and 2) and validation (epoch 3) sets for the outcomes of overall survival (A), relapse (B), and non-relapse mortality (C). The individual hazards associated with disease–status pairs are depicted in the appendix (p 9).



We developed a disease-risk stratification scheme categorising patients into three strata (low, intermediate, and high) on the basis of disease, time from diagnosis, disease status, and cytogenetics (as appropriate to the diagnosis) using patients from epochs 1 and 2 (appendix pp 9, 20). The scheme was validated on patients treated in epoch 3 (figure 3). In a multivariable Cox model comparing risk strata in the validation cohort, intermediate-risk and high-risk disease were associated with an increased hazard of overall mortality (HR 1·24 [95% CI 1·20–1·28] for intermediate risk and 2·29 [2·21–2·38] for high risk; appendix p 22).

To balance the potential benefit of greater alloimmunity with the concern for increased non-relapse mortality in non-matched sibling transplantations, we compared outcomes by donor type within each disease-risk stratum in the latest epoch. Matched sibling donors were the reference category.

Recipients of matched sibling transplantations had the lowest overall mortality risk across all disease-risk categories (figure 4A). In low-risk and intermediate-risk disease, the relative hazard for all-cause mortality was higher with matched unrelated transplantation (HR 1·22 [95% CI 1·16–1·28], p<0·0001 for low risk and 1·12 [1·05–1·20], p=0·0004 for intermediate risk).

The likelihood of non-relapse mortality was higher with matched unrelated transplantations compared with matched sibling transplantations in all disease-risk strata, most prominently in low-risk disease (HR 1·45, 95% CI 1·34–1·56; p<0·0001). Alternative donors had an even greater hazard for non-relapse mortality, with overlapping risk between donor types (figure 4B). Between 2011 and 2015, the leading cause of non-relapse mortality was infection in haploidentical (33·7%, 258/766) and cord blood (31·1%, 125/402) HSCT, and GVHD in recipients of matched sibling (36·3%, 925/2548), matched unrelated (31·7%, 1078/3397), and mismatched unrelated (32·0%, 387/1210) transplantations (appendix p 23). Graft rejection as the cause of non-relapse mortality was most prevalent in haploidentical transplantations (9·5%, 73/766) followed by mismatched unrelated (6·4%, 78/1210), cord blood (5·7%, 23/402), matched unrelated (5·4%, 183/3397), and matched sibling (3·5%, 89/2548) HSCT.

Matched unrelated HSCT was associated with decreased relapse in the low-risk (HR 0·89, 95% CI 0·84–0·95; p=0·0003) and intermediate-risk (0·86, 0·80–0·92; p<0·0001) disease strata, although not in high-risk

Figure 4: **Outcomes by donor type and risk status**
Hazard ratios shown on the horizontal axis in log-scale. Cox regression multivariable models are constructed separately for each donor category. Models are adjusted for patient age, recipient and donor cytomegalovirus serostatus, female donor to male recipient status, time from diagnosis to transplantation, and conditioning intensity, with centre as a random effect. The numbers of cases and events represent the mean across imputations. Unadjusted (univariable) results are presented in the appendix (p 29).

disease (0·91, 0·83–1·00; p=0·059). The hazard of relapse in recipients of haploidentical transplantations was 0·83 (95% CI 0·73–0·96; p=0·011) in those with low-risk disease and 0·85 (0·74–0·99; p=0·033) in those with intermediate-risk disease (figure 4C), whereas no benefit was observed in the high-risk setting (1·14, 1·00–1·30; p=0·053).

Recipients of grafts from matched unrelated donors experienced similar risk for a progression-free survival event to recipients of matched sibling donor grafts in both intermediate-risk and high-risk disease (figure 4D). Haploidentical, cord blood, and mismatched unrelated transplantations had consistently higher risk than did matched sibling transplantations for a progression-free survival event (figure 4D).

In a sensitivity analysis assessing the effect of missing HLA match information among unrelated donors, results were broadly consistent with findings above, suggesting the models are robust (appendix pp 5, 11, 13). To include as many recipients as possible for the temporal evaluation of outcomes, we defined matched unrelated donors as donors matched in 8/8 *HLA* alleles (A, B, C, and DR) with recipients. The contemporary standard for matched unrelated donors in the EBMT is compatibility at 10/10 alleles, including DQ. Among the 25 007 patients we defined as recipients of matched unrelated HSCT, 23 184 (92·7%) were matched at a 10/10 level, 1065 (4·3%) had DQ mismatch, and 758 (3·0%) had no information on DQ alleles. When repeating the analysis of the donor-associated hazard stratified by disease risk with matched unrelated donors defined by 10/10 alleles instead of 8/8, results were consistent (data not shown), suggesting that our findings are applicable to current practice. Post-transplantation cyclophosphamide and anti-thymocyte globulin-based haploidentical transplantation were also studied separately, yielding similar estimates of risk (appendix p 24). Because the highest risk of mortality occurred in the first year following transplantation, we did a landmark analysis of patients alive and relapse-free at 1 year. We found no continued overall survival benefit of matched sibling donors over other donors beyond the first year, except relative to mismatched unrelated donors (appendix p 25).

Discussion

The rise of unrelated and haploidentical donors represents a pivotal change in the field of allogeneic stem cell transplantation over the past two decades. Transplantation is now an option for an increasing number of patients. This change prompted us to evaluate trends in outcomes across donor categories. Our study shows that overall survival improved over time across all donor types. Improved survival seems to be primarily driven by a reduction in non-relapse mortality, except in cord blood transplantation, where a lower likelihood of relapse accounts for improvement. Among patients treated between 2011 and 2015, depending on donor type, 24–33% of recipients were alive and free of relapse or extensive GVHD at 3 years post transplantation. In line with the hypothesis that donor–recipient HLA disparity affects disease control, we find that disease aggressiveness should be considered when selecting a donor. Among patients transplanted in the most recent epoch with low-risk or intermediate-risk disease, matched sibling HSCT was associated with the lowest hazard for mortality. In the high-risk disease setting, however, recipients of matched unrelated HSCT had similar hazard for mortality to those of matched sibling HSCT. In the latter scenario, increased non-relapse mortality was balanced by a reduction in relapse. Recipients of haploidentical transplantations with low-risk and intermediate-risk disease were also less likely to relapse, holding substantial promise if non-relapse mortality can be further controlled.

Since the early 2000s, recipient age has gradually increased. Nevertheless, survival is improving with all donor types, continuing a previously reported trend.[7] Reduction in non-relapse mortality was the driving force behind improved survival in most donor types. Contributing factors to this reduction might be the widespread use of reduced-intensity conditioning (50% in epoch 3) and better supportive care.[5,6] Notably, the greatest reduction in non-relapse mortality across all transplantation types was observed among recipients of haploidentical HSCT, going down from 39·8% in epoch 2 to 27·3% in epoch 3. Widespread use of post-transplantation cyclophosphamide, surpassing anti-thymocyte globulin, is likely to account for this marked improvement. Post-transplantation cyclophosphamide has been shown to be a safe and effective technique to overcome the HLA disparity barrier,[10] and its extension to other donors is appealing.[19]

The tenacity of relapse over time across donor types might reflect selection of patients with resistant diseases for transplantation. Effective targeted therapies in chronic myeloid leukaemia, lymphoma, and multiple myeloma have abrogated the need for early HSCT. Notably, in recipients of cord blood HSCT, relapse incidence fell from 35% to 29% between the last two epochs despite accounting for changes in patient and disease characteristics over time using inverse probability weighting. Similar trends were also seen when analysing single-unit and double-unit cord blood transplantation separately (appendix p 17). This change might be related to latent covariates and warrants further investigation. Although a stubborn barrier, there is new optimism for overcoming relapse. Augmenting allogeneic HSCT with tyrosine kinase inhibitors, epigenetic and immune modulation, and cellular therapies could prove valuable.[20]

Despite the widespread use of peripheral blood cells grafts and older recipient age, both established risk factors for chronic GVHD,[21] the incidence of extensive chronic GVHD is declining. Controlling for graft source

is unlikely to alter the reduction between epochs 2 and 3 since more than 80% of our patients received peripheral blood grafts. A plausible explanation for the improvement is the increasing use of anti-thymocyte globulin,[22] which has been widely adopted in EBMT centres. Anti-thymocyte globulin was the predominant haploidentical strategy in epoch 2 (75%), supplanted by post-transplantation cyclophosphamide in epoch 3 (76%). Occurrence of severe acute and extensive chronic GVHD remained similar despite this shift in practice, suggesting that both techniques are valid for GVHD prevention. A reduction in severe acute GVHD was seen in the second epoch for recipients of matched sibling HSCT; increased use of reduced-intensity conditioning and combinations of calcineurin inhibitors and methotrexate are probably responsible for this result.[23] In recipients of cord blood HSCT, severe acute GVHD was more common in epoch 3, possibly reflecting a rise in double-unit cord blood transplantation.[24] Since outcomes of cord blood transplantation, including GVHD, are dependent on cell dose in the graft and HLA typing, accounting for these variables could further refine results.[25] However, both cannot be studied independently of the number of cord blood units infused; insufficient data in the registry precluded these analyses. Overall, despite improvement in specific outcomes across donor types, GVHD-free, relapse-free survival, a measure reflecting an ideal outcome, is achieved by only approximately 30% of patients. High-resolution HLA matching, biomarker-driven approaches, modification of the gut microbiota, and targeted immunosuppression are all promising strategies that might further reduce GVHD and improve overall survival and quality of life.[26,27]

The graft-versus-tumour effect, induced by alloimmune donor T cells, is essential for the success of allogeneic HSCT. Evidence for graft-versus-tumour effect includes a lower incidence of relapse in recipients experiencing GVHD, higher relapse rates after syngeneic and T cell-depleted transplantation, remission induction by infusion of donor lymphocytes, and durable remission following reduced-intensity conditioning regimens.[3] In theory, greater HLA disparity between donor and recipient could also mitigate relapse risk, but this has not been consistently reported.[9,28] Furthermore, bidirectional alloreactivity increases the risk of GVHD and graft failure, resulting in increased non-relapse mortality. Weighing the likelihood of relapse versus non-relapse mortality could guide donor selection. Therefore, we developed a disease risk stratification scheme for overall mortality based on various combinations of disease and disease status, following Armand et al[12] with several modifications. This system could have benefited from additional molecular data that were not available. However, increasing incidence of relapse drove a stepwise decrease in overall survival between the three risk groups we defined, showing the scheme's validity.

In an analysis restricted to the latest epoch, recipients of matched sibling HSCT had the lowest risk for non-relapse mortality in all disease-risk categories. Compared with the other donor types, excluding mismatched unrelated, this advantage was only evident in the first year following transplantation. Importantly, recipients of matched unrelated transplantation were less prone to relapse in all disease-risk strata, suggesting a graft-versus-tumour effect. Although other studies have not found such an association, our analysis is probably powered to detect it. Minor HLA-antigen mismatch in otherwise-matched unrelated donors might contribute to greater alloimmunity against the tumour.[29] In high-risk disease, this tension between non-relapse mortality and relapse translated into recipients of matched unrelated and matched sibling HSTC having equivalent hazards for progression-free survival events. Overall survival was improved with matched sibling donors in the other disease-risk strata. Prospective trials targeting patients with high-risk disease, comparing matched unrelated donors and matched sibling donors with additional covariates (donor age,[30] killer-cell immunoglobulin-like receptor matching,[31] higher resolution HLA-typing[4,27]) could further illuminate the role of donor selection in this population. Compared with recipients of matched sibling transplantations, relapse risk was also lower in recipients of haploidentical transplantations in low-risk and intermediate-risk disease, supporting a graft-versus-tumour effect in the haploidentical setting. Notably, in high-risk patients, haploidentical transplantation was not associated with a reduction in relapse. Aggressive malignant cells might be more likely to escape anti-tumour T cells from haploidentical grafts by losing the mismatched HLA haplotype.[32] Alternatively, this effect could be related to a slower alloimmune effect and rapid relapses in highly proliferative disease.

Measurement and selection biases are inescapable limitations of retrospective registry studies. To minimise selection bias, we chose to include nearly all patients reported to the registry. Therefore, our findings reflect real-life experience throughout most transplant centres in Europe and can be used to inform decision making. Missing HLA-match status among unrelated donors, especially in the first epoch, also limits our analysis. Nevertheless, by using multiple imputations and doing sensitivity analyses under a variety of assumptions, we show that the findings we have presented are robust. Other potential limitations of the study include generalisability of the results outside Europe, as well as considering disease-risk stratification as fixed three-levels groups. The categorisation of disease-risk, rather than using it as continuous measure, leads to loss of prognostic information. However, defined risk groups enabled comparison of donor types in individual disease-risk strata.

Increasing donor availability has resulted in more than half a million allogeneic transplantations since

E Donnall Thomas and colleagues pioneered the therapy more than 60 years ago. Our analysis shows a continued trend of improving overall survival potentially driven by decreasing non-relapse mortality, most prominently with haploidentical transplants, suggesting a learning curve and advancement in supportive care. Nevertheless, relapse remains a stubborn barrier. We anticipate that disease control will improve with greater use of immunomodulatory approaches. Importantly, the traditional hierarchy of donors still holds, with a matched sibling donor being the best option for most patients. However, in recipients with high-risk disease, a matched unrelated donor might be equivalent. Prospective trials evaluating donor selection in the context of relapse risk could lead to strategies for better disease control, optimising the risk–benefit ratio of allogeneic HSCT.

Contributors

RS, JAF, and AN conceived the study. RS, JAF, and ML were responsible for the methods and data analysis. J-EG contributed to the methodology used for multiple imputation analyses. RS, JAF, and AN wrote the first draft of the manuscript. EP was responsible for data management. NK, RFD, PB, CC, JK, GB, CD, AL, SM, JAS, JS, IYA, and MM, interpreted, critically evaluated, and improved the study design and manuscript.

Declaration of interests

RFD reports personal fees and non-financial support from Merck Sharp & Dohme, Jazz Pharmaceuticals, Gilead Sciences, Omeros Pharmaceuticals, and MEDAC; and personal fees from Cidara and Therakos, outside of the submitted work. JK reports grants from Miltenyi and other support from Novartis and Gadeta, during the conduct of the study; and reports grants from Miltenyi, Novartis, and Gadeta, outside of the submitted work. JK has also been a scientific advisor for Gadeta and is a shareholder. GWB reports other support from Saventic Health, grants and personal fees from Genzyme, and personal fees from Merck Sharp & Dohme, Astellas, Takeda, Celgene, Novartis, and Gilead, outside of the submitted work. SM reports other support from Bayer and Gilead, outside of the submitted work. JAS reports personal fees from Janssen, Jazz Pharmaceuticals, Kiadis Pharma, and NHS England, outside of the submitted work. All other authors declare no competing interests.

Data sharing

For study data, contact the corresponding author.

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