Development and validation of a disease risk stratification system for patients with haematological malignancies: a retrospective cohort study of the European Society for Blood and Marrow Transplantation registry

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Summary

Background Diagnosis and remission status at the time of allogeneic haematopoietic stem-cell transplantation (HSCT) are the principal determinants of overall survival following transplantation. We sought to develop a contemporary disease-risk stratification system (DRSS) that accounts for heterogeneous transplantation indications.

Methods In this retrospective cohort study we included 55 histology and remission status combinations across haematological malignancies, including acute leukaemia, lymphoma, multiple myeloma, and myeloproliferative and myelodysplastic disorders. A total of 47265 adult patients (aged ≥18 years) who received an allogeneic HSCT between Jan 1, 2012, and Dec 31, 2016, and were reported to the European Society for Blood and Marrow Transplantation registry were included. We divided EBMT patients into derivation (n=25534), tuning (n=18365), and geographical validation (n=3366) cohorts. Disease combinations were ranked in a multivariable Cox regression for overall survival in the derivation cohort, cutoff for risk groups were evaluated for the tuning cohort, and the selected system was tested on the geographical validation cohort. An independent single-centre US cohort of 660 patients transplanted between Jan 1, 2010, and Dec 31, 2015 was used to externally validate the results.

Findings The DRSS model stratified patients in the derivation cohort (median follow-up was 2·1 years [IQR 1·0–3·2]) into five risk groups with increasing mortality risk: low risk (reference group), intermediate-1 (hazard ratio for overall survival 1·26 [95% CI 1·17–1·36], p<0·0001), intermediate-2 (1·53 [1·42–1·66], p<0·0001), high (2·03 [1·86–2·22], p<0·0001), and very high (2·87 [2·63–3·13], p<0·0001). DRSS levels were also associated with a stepwise increase in risk across the tuning and geographical validation cohort. In the external validation cohort (median follow-up was 5·7 years [IQR 4·5–7·1]), the DRSS scheme separated patients into 4 risk groups associated with increasing risk of mortality: intermediate-2 risk (hazard ratio [HR] 1·34 [95% CI 1·04–1·74], p=0·025), high risk (HR 2·03 [95% CI 1·39–2·95], p=0·00023) and very-high risk (HR 2·26 [95% CI 1·62–3·15], p<0·0001) patients compared with the low risk and intermediate-1 risk group (reference group). Across all cohorts, between 64% and 65% of patients were categorised as having intermediate-risk disease by a previous prognostic system (ie, the disease-risk index [DRI]). The DRSS reclassified these intermediate-risk DRI patients, with 855 (6%) low risk, 7111 (51%) intermediate-1 risk, 5700 (41%) intermediate-2 risk, and 375 (3%) high risk or very high risk of 14041 patients in a subanalysis combining the tuning and internal geographic validation cohorts. The DRI projected 2-year overall survival was 62·1% (95% CI 61·2–62·9) for these 14041 patients, while the DRSS reclassified them into finer prognostic groups with overall survival ranging from 45·7% (37·4–54·0; very high risk patients) to 73·1% (70·1–76·2; low risk patients).

Interpretation The DRSS is a novel risk stratification tool including disease features related to histology, genetic profile, and treatment response. The model should serve as a benchmark for future studies. This system facilitates the interpretation and analysis of studies with heterogeneous cohorts, promoting trial-design with more inclusive populations.

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Introduction

Relapse remains a stubborn barrier to successful allogeneic haematopoietic stem-cell transplantation (HSCT), occurring in nearly a third of transplantations.[1] Diagnosis and remission status at the time of transplantation are among the strongest predictors of relapse and death.[1–4]

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See **Comment** page e166

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Research in context

Evidence before this study

We searched PubMed for the terms ("disease risk") OR ("disease status") AND ("allogeneic stem-cell transplantation") in reports published in any language from database inception up to Aug 9, 2020, to identify relevant published clinical data. We found several prognostic systems that incorporated disease and disease status to stratify patients by risk of overall mortality. Up until August, 2020, the revised Disease Risk Index (DRI) was the most comprehensive and widely used. The DRI has been successfully applied in retrospective and prospective studies. However, the DRI was developed on transplants done between the years 2008 and 2010 and does not reflect subsequent changes in patients and disease profiles. In addition, the DRI does not capture informative features in acute myeloid leukaemia, such as disease origin, molecular features (eg, *FLT3* and *NPM1* mutations), and specific cytogenetic aberrations that are known to affect outcome. Finally, across studies implementing the DRI, approximately 70% of patients were classified as being intermediate risk, limiting the system's ability to discriminate between patients who are classified as truly high and patients who are classified as being low risk who could benefit from targeted interventions.

Added value of this study

In this large international registry-based study, we developed and internally and externally validated a disease-risk stratification system for overall survival, grouping 55 combinations of disease and disease status into five risk tiers. An increasing tendency to relapse drives the incremental risk of mortality between tiers. To our knowledge, this is the first global prognostic system which subdivides acute myeloid leukaemia, the leading allogeneic transplant indication, by ontology (ie, de-novo *vs* secondary), cytogenetics, and *FLT3* and *NPM1* mutational status. The new system reclassifies patients previously considered to have intermediate-risk disease by the DRI into finer, potentially actionable, prognostic categories. Finally, to our knowledge, our study is the most comprehensive and most recent prognostic system for patients with haematological malignancies undergoing allogeneic transplantation. It was developed, optimised, and validated on 47 925 patients, highlighting its robustness and generalisability.

Implications of all the available evidence

Our system reflects an up-to-date approach for risk stratification in patients with haematological malignancies undergoing allogeneic haematopoietic stem-cell transplantation. It facilitates the interpretation and analysis of prospective and retrospective studies with heterogeneous cohorts, promoting the design of non-disease-specific trials with broader, more inclusive populations. The system should also serve the medical community as a benchmark for transplantation outcomes in the coming years. Our approach lays the foundation for further iterations of this prognostic system, which will incorporate more detailed molecular information and data for measurable residual disease, both of which are increasingly being captured in transplantation registries.

Accounting for these factors is imperative when contemplating transplantation, designing a clinical trial, or analysing outcomes.

To standardise the process of pre-transplantation risk assessment, prognostic systems have categorised risk on the basis of the combination of disease and remission status.[2,3,5–7] The disease-risk index (DRI)[2,3] has proven valuable and is considered the standard for prognostication in cohorts with heterogeneous diagnoses.[8,9] Nevertheless, the DRI was developed on patients who were transplanted over a decade ago and assigns the bulk of recipients to the intermediate-disease-risk category.[2,3] Ideally, a prognostic model would reflect more recent practice and provide finer, actionable categories. Therefore, we sought to develop and validate a more contemporary disease-risk stratification system (DRSS) for patients with haematological malignancies undergoing allogeneic HSCT. Such a system could promote the design of non-disease-specific trials by accounting for the population's heterogeneity, increasing power and generalisability of results. Furthermore, the DRSS could contribute to the analysis and interpretation of prospective and retrospective studies.

Methods

Study design and data sources

The European Society for Blood and Marrow Transplantation (EBMT) maintains an audited registry of HSCT done by member-institutions. Over 600 participating centres, located mainly in Europe, submit anonymised data following patient informed consent. For model development and internal validation, we included 47 265 adult allogeneic HSCT recipients (aged ≥18 years) with haematological malignancies reported to the registry between Jan 1, 2012, and Dec 31, 2016. For external validation, we included 660 patients transplanted at the Memorial Sloan Kettering Cancer Center (MSKCC) between Jan 1, 2010, and Dec 31, 2015. Patients receiving cord blood grafts or cells from HLA-mismatched related donors were not included in the MSKCC cohort.

We divided EBMT patients into derivation (n=25 534), tuning (n=18 365), and geographical validation (n=3366) cohorts.[10] Briefly, combinations of disease and remission status were studied and ranked according to mortality risk on the derivation cohort, which included patients transplanted between Jan 1, 2014, and Dec 31, 2016. As there is no so-called ground truth for defining risk groups, we generated several potential risk groups

schemes on the derivation cohort and evaluated them on the tuning cohort, which included EBMT patients transplanted between Jan 1, 2012, and Dec 31, 2014. The selected scheme was then tested on the internal geographical validation and external validation cohorts, which were held throughout the training and tuning process. The internal geographical validation cohort comprised patients transplanted between Jan 1, 2014, and Dec 31, 2016, in Italian centres reporting to the EBMT and the external validation cohort was a cohort transplanted at MSKCC between Jan 1, 2010, and Dec 31, 2015. A schematic overview of the analytic plan is provided in the appendix (p 16).

Donor types and conditioning intensities were defined as previously described,[1] following the EBMT working definitions. Briefly, 15 haematological malignancies were considered and further stratified by disease status at the time of transplantation. Additional genetic markers were studied for acute myeloid leukaemia, acute lymphoblastic leukaemia, and myelodysplastic syndrome. Acute myeloid leukaemia was first classified as de-novo or secondary on the basis of standard criteria.[11,12] Cytogenetic risk definition in acute myeloid leukaemia was based on the European Leukemia Net definitions (appendix p 2),[13] and patients in the intermediate-risk cytogenetic with de-novo acute myeloid leukaemia group were stratified by *FLT3*-ITD (FMS-like tyrosine kinase-3 internal tandem duplication) and *NPM1* (nucleophosmin-1) mutation status. Myelodysplastic syndrome was considered to have adverse cytogenetic risk features in patients with complex karyotype (≥3 chromosomal abnormalities) or the deletion or monosomy of chromosome 7.[2] For acute lymphoblastic leukaemia, categorisation by the Philadelphia chromosome (Ph; t(9;22)(q34;q11) and *BCR-ABL1*) and t(4;11) and *KMT2A-AFF1* were evaluated. As transplantation studies often have high rates of missing cytogenetic information, we kept missing cytogenetics in acute myeloid leukaemia, myelodysplastic syndrome, and acute lymphoblastic leukaemia as separate levels.

The Acute Leukemia Working Party, the EBMT Scientific Council, and MSKCC's Institutional Review Board approved this study in accordance with the Declaration of Helsinki.

Outcomes

The studied outcome was overall survival, measured from the time of stem-cell infusion to censoring or death from any cause. Relapse and non-relapse mortality were also assessed as competing events.

Statistical analysis

In the first stage, disease and disease status pairs were constructed following the example outlined in the DRI.[2,3] New subcategories of clinical interest were added when sub-histologies had distinct survival outcome ($p<0·05$), as assessed by hazard ratio (HR) adjusted for recipient age, Karnofsky performance status, conditioning intensity, donor and cell type, donor and recipient sex mismatch, and cytomegalovirus serostatus pair with a random effect for centre in the derivation set. These changes included the division of acute myeloid leukaemia into de-novo and secondary acute myeloid leukaemia (as the de-novo acute myeloid leukaemia category was associated with better overall survival), separation of de-novo acute myeloid leukaemia into patients' first complete remission and subsequent complete remission, stratification of de-novo acute myeloid leukaemia in patients' first complete remission with intermediate cytogenetics based on *FLT3*-ITD and *NPM1* status (to *FLT3*-ITD^{+} and *NPM1*^{WT} *vs* all other combinations), stratification of de-novo acute myeloid leukaemia in patients' subsequent complete remission based on adverse cytogenetics and *FLT3*-ITD status, stratification of secondary acute myeloid leukaemia in patients' complete remission on the basis of adverse cytogenetics, and stratification of acute lymphoblastic leukaemia in patients' first complete remission based on t(9;22) status (appendix p 17). We explored and rejected the inclusion of t(4;11) in acute lymphoblastic leukaemia in patients' first complete remission, as we did not find an association with differential survival (HR 1·32 [95% CI 0·83–2·10]; $p=0·24$). Within acute myeloid leukaemia, myelodysplastic syndrome, and acute lymphoblastic leukaemia in patients' first complete remission, patients with unknown cytogenetics were categorised separately. Finally, we added biphenotypic acute leukaemia in patients' complete remission and the myelodysplastic or myeloproliferative neoplasm overlap syndrome (myelodysplastic syndrome and myeloproliferative neoplasm) as new diagnoses.

See Online for appendix

We constructed a mixed-effects multivariable Cox regression model for overall survival using the derivation set, with disease-disease status pair adjusted for recipient age, Karnofsky performance status, conditioning intensity, donor and cell type, donor and recipient sex mismatch, and cytomegalovirus serostatus pair with a random effect for centre. The β-coefficients of the disease and status pairs were ranked. To create a risk stratification system that would be easily applied, we sought β-coefficients cutoff points that would produce groups comprising between 10% and 40% of patients and incrementally predictive of mortality. We generated several different sets of cutoff points over the derivation cohort, which were selected by serially searching for optimal cutoff points using the maximally selected log-rank statistic;[14] a method typically applied for identifying potential cutoff points in continuous covariates. Grouping schemes fitting our initial criteria were evaluated on the tuning cohort. The one scheme that resulted in clinically rational, homogeneous groups was then studied using a multivariable Cox regression model, adjusting for the same covariates as described for the disease-disease status pairs in this section (aside from centre effect on the single-centre validation cohort), on two datasets—the internal geographical validation and external validation cohorts (appendix p 16).

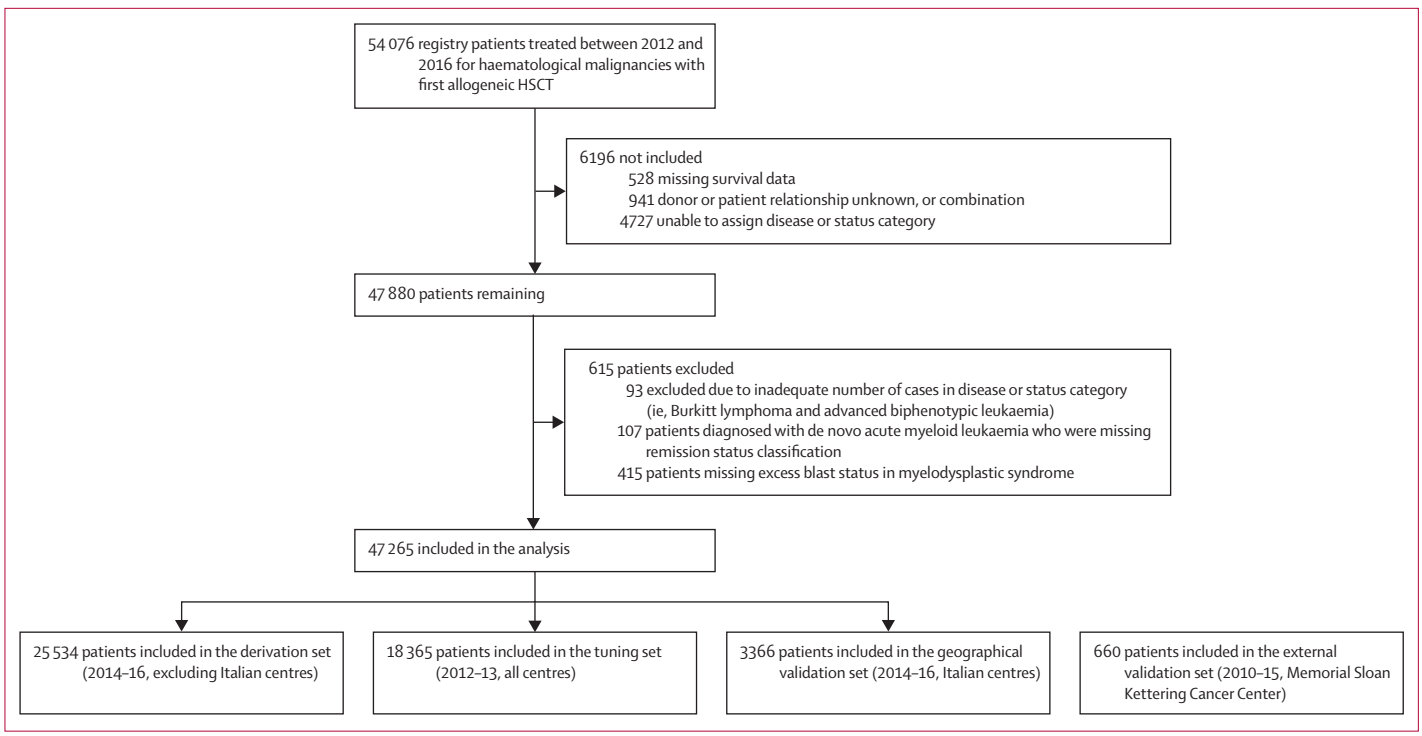

Figure 1: **Study profile**
The European Society for Blood and Marrow Transplantation cohort was split into derivation, tuning, and geographical validation cohorts. A cohort from Memorial Sloan Kettering Cancer Center served for external validation. HSCT=haematopoietic stem-cell transplantation.

For more on **DRSS outputs** see https://joshuafein.shinyapps.io/drss_calculator/

Overall survival was calculated using the Kaplan-Meier method and compared by the log-rank statistic. All p values were two-sided and values less than 0·05 were considered significant without adjustment for multiple testing. Discrimination of the new system was compared with the revised DRI[3] using time-dependent area under the receiver operating characteristic curve (AUC) statistic.[15] Analyses were done using SPSS (version 25.0) and R (v.3.5.3).

Role of the funding source

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

Results

Out of 54076 patients in the EBMT registry, patients with missing overall survival status (n=528) or donor relationship (n=941) or with insufficient information to establish diagnosis and disease status (n=4727) were excluded (figure 1). An additional 522 patients were dismissed because of disease-specific missing information and 93 because of the rarity of patients (sample size <50) in that diagnosis or status category (ie, Burkitt lymphoma and relapsed biphenotypic leukaemia). The final study population comprised of 47 265 patients. The median age of patients in the derivation cohort was 53 years (IQR 41–62; table 1). Acute myeloid leukaemia was the primary indication for transplantation, accounting for 11 881 (47%) of 25 534 patients, followed by acute lymphoblastic leukaemia (3474 patients; 13·6%), and myelodysplastic syndrome (2977 patients; 11·7%).

Bone marrow grafts (occurring in 1128 [33·5%]), haploidentical donors (occurring in 897 [26·6%]), and myeloablative conditioning (occurring in 2494 [74·1%]) were more prevalent in the geographical-validation cohort (n=3366 patients) compared with the derivation cohort (n=25 534; 2126 [8·3%] for bone marrow grafts, 1762 [6·9%] for haploidentical donors, and 12 476 [48·9%] for myeloablative conditioning). Median follow-up and completeness of follow-up[16] at 2 years was 2·1 years (IQR 1·0–3·2) and 72·7% for the derivation cohort, 4·6 years (1·9–5·6) and 83·8% for the tuning cohort, and 3·0 years (2·3–3·9) and 94·8% for the geographical validation cohort.

On the derivation set, 55 possible disease and disease status-based combinations were studied in a multivariable Cox model. De-novo acute myeloid leukaemia in patients' first complete remission with intermediate-risk cytogenetics and without the *FLT3*-ITD^{+} and *NPM1*^{WT} mutations was selected as the reference. The proportional increase of the adjusted hazard, relative to this reference, is shown in figure 2 (appendix p 3). To generate a prognostic scheme, which we refer to as the

DRSS, disease and disease-status pairs were grouped by β-coefficient and thresholds were selected as described in the statistical analysis section in the Methods section. Several possible risk grouping schemes were generated on the derivation cohort and evaluated on the tuning cohort. Based on the criteria described in the Methods, the selected 5 levels scheme (ie, low risk, intermediate-1 risk, intermediate-2 risk, high risk, and very-high risk groups) classified 3298 (13%) of the total 25534 patients in the derivation cohort as low-risk, 9528 (37%) patients in the derivation cohort as intermediate-1 risk, 7072 (28%) patients in the derivation cohort as intermediate-2 risk, 2546 (10%) patients in the derivation cohort as high risk, and 3090 (12%) patients in the derivation cohort as very-high risk.

Over the derivation set, risk levels were associated with a monotonic independent increase in the HR for overall mortality (table 2, appendix p 5). This risk corresponded to unadjusted 2-year overall survival rates of 72·4% (95% CI 70·7–74·1; low risk), 64·1% (62·9–65·2; intermediate-1 risk), 57·6% (56·3–58·9; intermediate-2 risk), 47·6% (45·4–49·8; high risk), and 36·2% (34·3–38·2; very high risk; figure 3A, appendix p 6). The increasing risk of transplantation failure was driven primarily by relapse (appendix pp 6–8).

An online interface for calculating the DRSS category and providing disease and disease status specific unadjusted overall survival curves (appendix pp 19–37) is available.

The distribution of the DRSS over the tuning and geographical validation cohorts was similar to the derivation cohort. In the tuning cohort, the low risk category consisted of 1653 (9%) of 18365 total patients, the intermediate-1 risk category consisted of 7019 (38%) patients, the intermediate-2 risk category consisted of 5655 (31%) patients, the high risk category consisted of 1568 (9%) patients, and the very high risk category consisted of 2470 (13%) patients, compared with 328 (10%; low risk), 1314 (39%; intermediate-1 risk), 894 (27%; intermediate-2 risk), 342 (10%; high risk), and 488 (14%; very high risk) of 3366 patients in the geographical validation cohort. Risk of death and relapse also followed the same pattern as in the derivation cohort, with DRSS being the strongest predictor of survival (figure 3B,C, table 2, appendix pp 5, 7–8). Over the tuning and geographical validation cohorts, the HRs for overall mortality of the intermediate-1 risk group were 1·25 (95% CI 1·14–1·37; p<0·0001) and 1·48 (1·17–1·88, p=0·0011); intermediate-2 risk group (1·52 [1·38–1·67] and 1·62 [1·27–2·08]; p<0·0001); high risk group (2·04 [1·83–2·28] and 2·61 [2·01–3·39]; p<0·0001); and very high risk group (2·90 [2·62–3·22] and 3·70 [2·88–4·74]; p<0·0001). In a sensitivity analysis including in-vivo T cell depletion as a covariate in the Cox model (appendix p 9), the DRSS remained an independent predictor of survival in the geographical validation cohort.

	Derivation cohort (2014–16)	Tuning cohort (2012–13)	Geographical validation cohort (2014–16)*
N	25534	18365	3366
Age, years (median [IQR])	53 (41–62)	51 (39–60)	52 (40–60)
Sex			
Male	15019 (58·8%)	10842 (59·0%)	1911 (56·8%)
Female	10459 (41·0%)	7488 (40·8%)	1453 (43·2%)
Unknown	56 (0·2%)	35 (0·2%)	2 (0·1%)
Karnofsky performance status			
≥90	17465 (68·4%)	13139 (71·5%)	2585 (76·8%)
<90	6172 (24·2%)	4017 (21·9%)	741 (22·0%)
Unknown	1897 (7·4%)	1209 (6·6%)	40 (1·2%)
Diagnosis			
Aggressive lymphoma†	1457 (5·7%)	1062 (5·8%)	211 (6·3%)
Acute lymphoblastic leukaemia‡	3474 (13·6%)	2699 (14·7%)	561 (16·7%)
Acute myeloid leukaemia	11881 (46·5%)	8248 (44·9%)	1578 (46·9%)
Chronic lymphocytic leukaemia	564 (2·2%)	768 (4·2%)	54 (1·6%)
Hodgkin disease	741 (2·9%)	599 (3·3%)	189 (5·6%)
Indolent lymphoma§	827 (3·2%)	751 (4·1%)	98 (2·9%)
Multiple myeloma	852 (3·3%)	783 (4·3%)	90 (2·7%)
Myelodysplastic syndrome	2977 (11·7%)	1700 (9·3%)	303 (9·0%)
Myeloproliferative neoplasms¶	2761 (10·8%)	1755 (9·6%)	282 (8·4%)
Cell source			
Bone marrow	2126 (8·3%)	2261 (12·3%)	1128 (33·5%)
Peripheral blood	22943 (89·9%)	15514 (84·5%)	2198 (65·3%)
Cord blood	465 (1·8%)	590 (3·2%)	40 (1·2%)
Donor			
Matched related	8492 (33·3%)	6718 (36·6%)	979 (29·1%)
Haploidentical relative	1762 (6·9%)	989 (5·4%)	897 (26·6%)
Matched unrelated (10/10)	7689 (30·1%)	5679 (30·9%)	747 (22·2%)
Mismatched unrelated (<10/10)	2071 (8·1%)	1988 (10·8%)	446 (13·3%)
Unknown match unrelated	5055 (19·8%)	2401 (13·1%)	257 (7·6%)
Unrelated cord blood	465 (1·8%)	590 (3·2%)	40 (1·2%)
Sex-match			
Not female-to-male	20432 (80·0%)	14359 (78·2%)	2577 (76·6%)
Female-to-male	4565 (17·9%)	3586 (19·5%)	707 (21·0%)
Unknown	537 (2·1%)	420 (2·3%)	82 (2·4%)
Cytomegalovirus serostatus pair			
Donor – / recipient –	6777 (26·5%)	4408 (24·0%)	346 (10·3%)
Donor – / recipient +	5330 (20·9%)	4234 (23·1%)	843 (25·0%)
Donor + / recipient –	2098 (8·2%)	1537 (8·4%)	233 (6·9%)
Donor + / recipient +	10289 (40·3%)	7421 (40·4%)	1782 (52·9%)
Unknown	1040 (4·1%)	765 (4·2%)	162 (4·8%)
Conditioning intensity			
Myeloablative	12476 (48·9%)	9964 (54·3%)	2494 (74·1%)
Reduced intensity	12400 (48·6%)	8050 (43·8%)	856 (25·4%)
Unknown	658 (2·6%)	351 (1·9%)	16 (0·5%)

Data are n (%) unless otherwise indicated. *Italian centres. †Includes patients with B-cell non-Hodgkin lymphomas and patients with T-cell non-Hodgkin lymphomas. ‡Includes patients with biphenotypic acute leukaemia. These patients are separate from patients with advanced biphenotypic acute leukaemia who were excluded due to rarity. §Includes patients with mantle cell lymphoma. ¶Includes patients with myelodysplastic syndrome or myeloproliferative neoplasm overlap.

Table 1: **The European Society for Blood and Marrow Transplantation population characteristics**

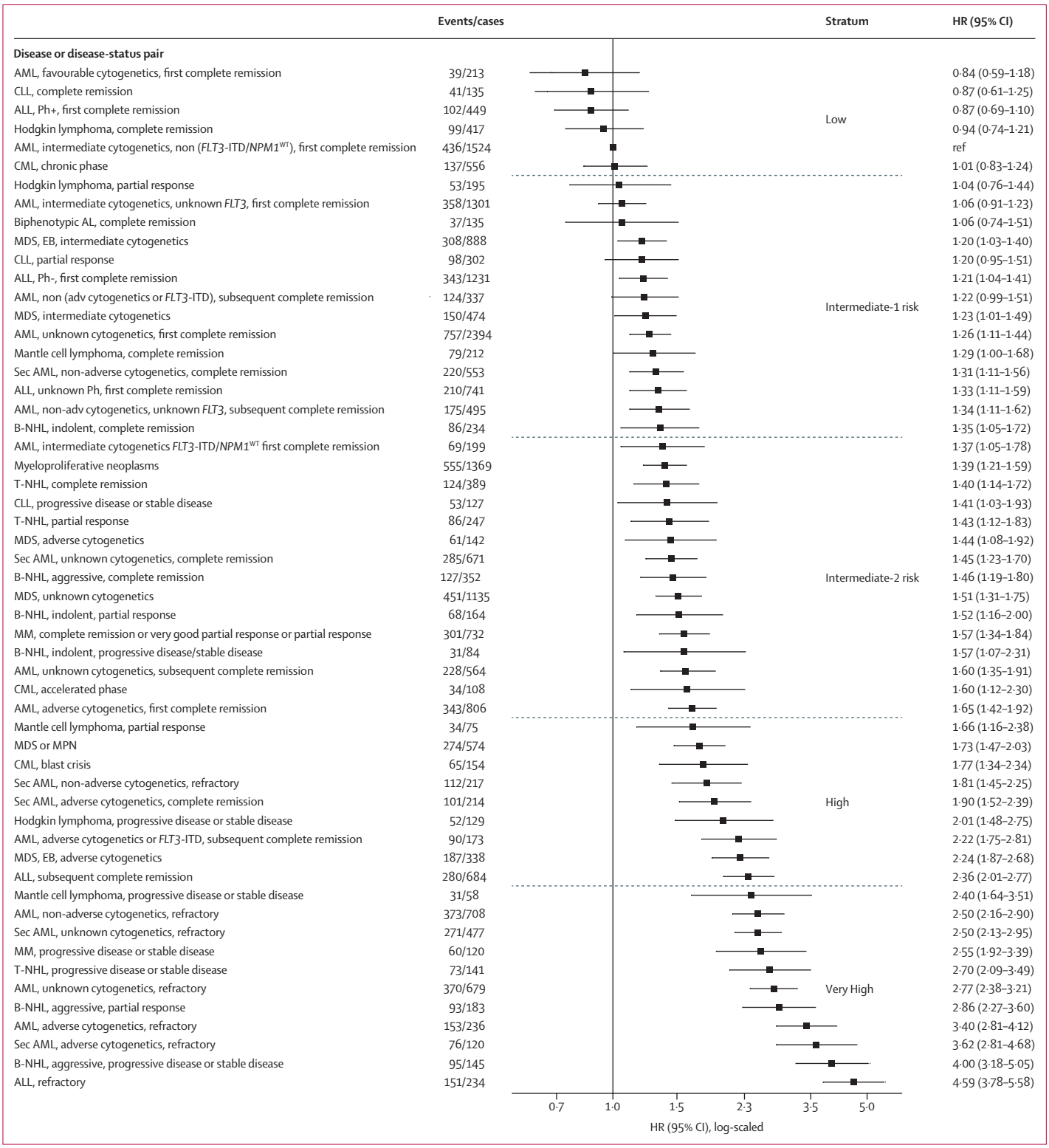

***Figure 2*: Disease-risk stratification system**

The hazard ratios for overall survival of multiple diseases and disease-status combinations over the derivation set are plotted. Combinations were divided into five risk groups. adv=adverse cytogenetics. AL=acute leukaemia. ALL=acute lymphoblastic leukaemia. AML=acute myeloid leukaemia. B-NHL=B-cell non-Hodgkin lymphoma. CLL=chronic lymphocytic leukaemia. CML=chronic myelogenous leukaemia. EB=excess blasts. ITD=internal tandem duplication. MDS=myelodysplastic syndrome. MM=multiple myeloma. MPN=myeloproliferative neoplasm. Ph=Philadelphia chromosome. sec=secondary disease. T-NHL=T-cell non-Hodgkin lymphoma.

	Derivation cohort			Tuning cohort			Geographic validation cohort		
	Cases/ events	HR (95% CI)	p value	Cases/ events	HR (95% CI)	p value	Cases/ events	HR (95% CI)	p value
Low risk	854/3298	1 (ref)	..	538/1653	1 (ref)	..	81/328	1 (ref)	..
Intermediate-1 risk	2998/9528	1·26 (1·17–1·36)	<0·0001	2697/7019	1·25 (1·14–1·37)	<0·0001	485/1314	1·48 (1·17–1·88)	0·0011
Intermediate-2 risk	2816/7072	1·53 (1·42–1·66)	<0·0001	2608/5655	1·52 (1·38–1·67)	<0·0001	379/894	1·62 (1·27–2·08)	<0·0001
High risk	1195/2546	2·03 (1·86–2·22)	<0·0001	859/1568	2·04 (1·83–2·28)	<0·0001	190/342	2·61 (2·01–3·39)	<0·0001
Very high risk	1746/3090	2·87 (2·63–3·13)	<0·0001	1620/2470	2·90 (2·62–3·22)	<0·0001	343/488	3·70 (2·88–4·74)	<0·0001

HR=hazard ratio. *The full multivariable results for overall survival, relapse incidence and non-relapse mortality are presented in the appendix (pp 5, 7–8).

Table 2: **HRs for overall mortality by disease-risk stratification system stratum***

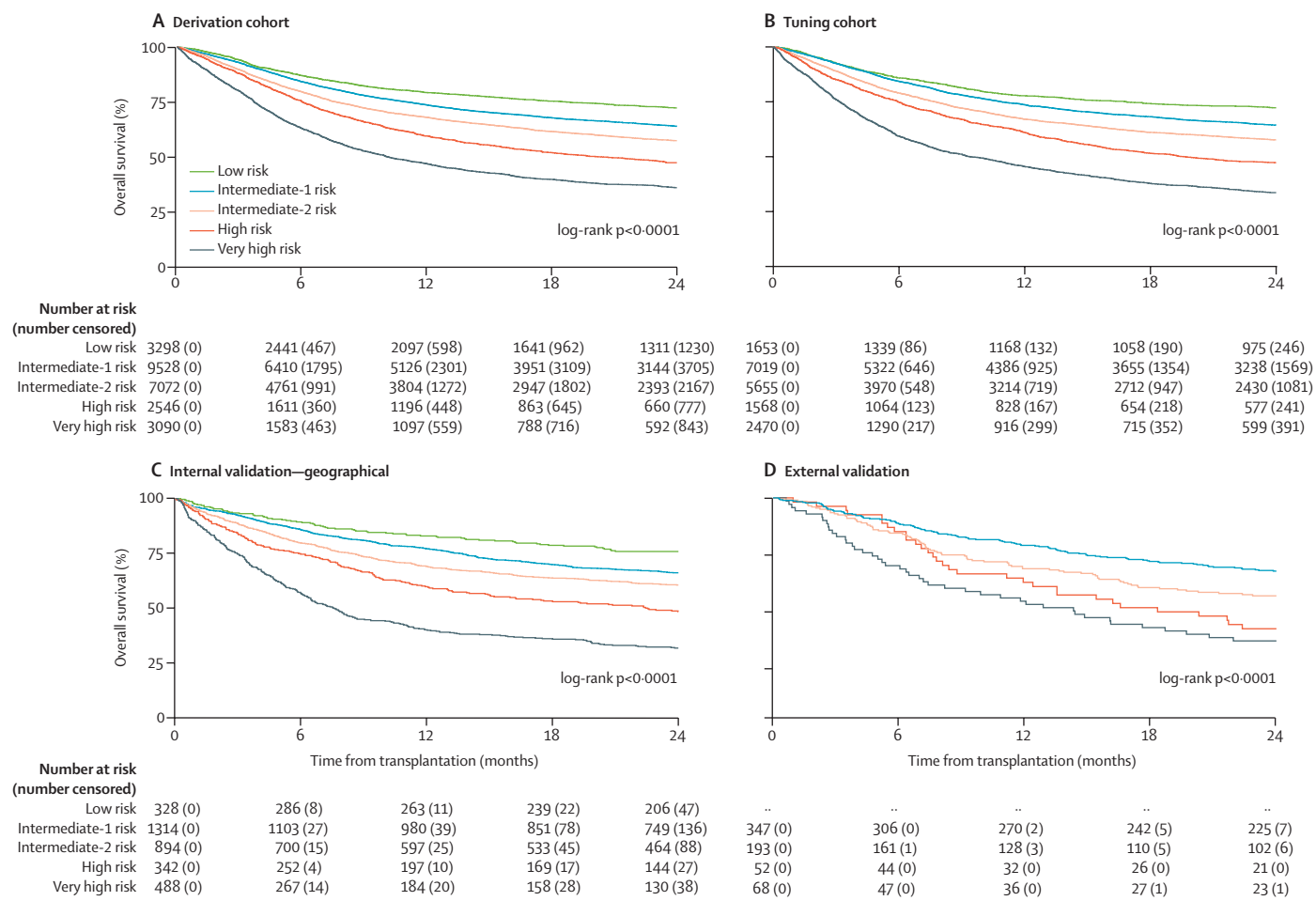

Figure 3: **Overall survival by the disease-risk stratification system (DRSS) and reclassification from the disease-risk index to the DRSS**
Overall survival by DRSS risk stratum is presented in the derivation (A), tuning (B), internal geographic validation (C), and external validation cohorts (D).

We studied an independent cohort of 660 patients transplanted at MSKCC (appendix p 10). Most (361 [55%] of 660) of the patients in this cohort received peripheral blood CD34 selected allografts, all of whom received myeloablative conditioning.[17] Acute myeloid leukaemia and myelodysplastic syndrome were the leading indications for transplantation, accounting for 207 (32%; acute myeloid leukaemia) and 115 (18%; myelodysplastic syndrome) of 660 patients. The median follow-up was 5·7 years (IQR 4·5–7·1) and completeness of 2-year follow-up was 98·8%. In this smaller cohort, there was no survival segregation between groups that were low risk and intermediate-1 risk, meaning that these groups were therefore merged. The condensed DRSS scheme

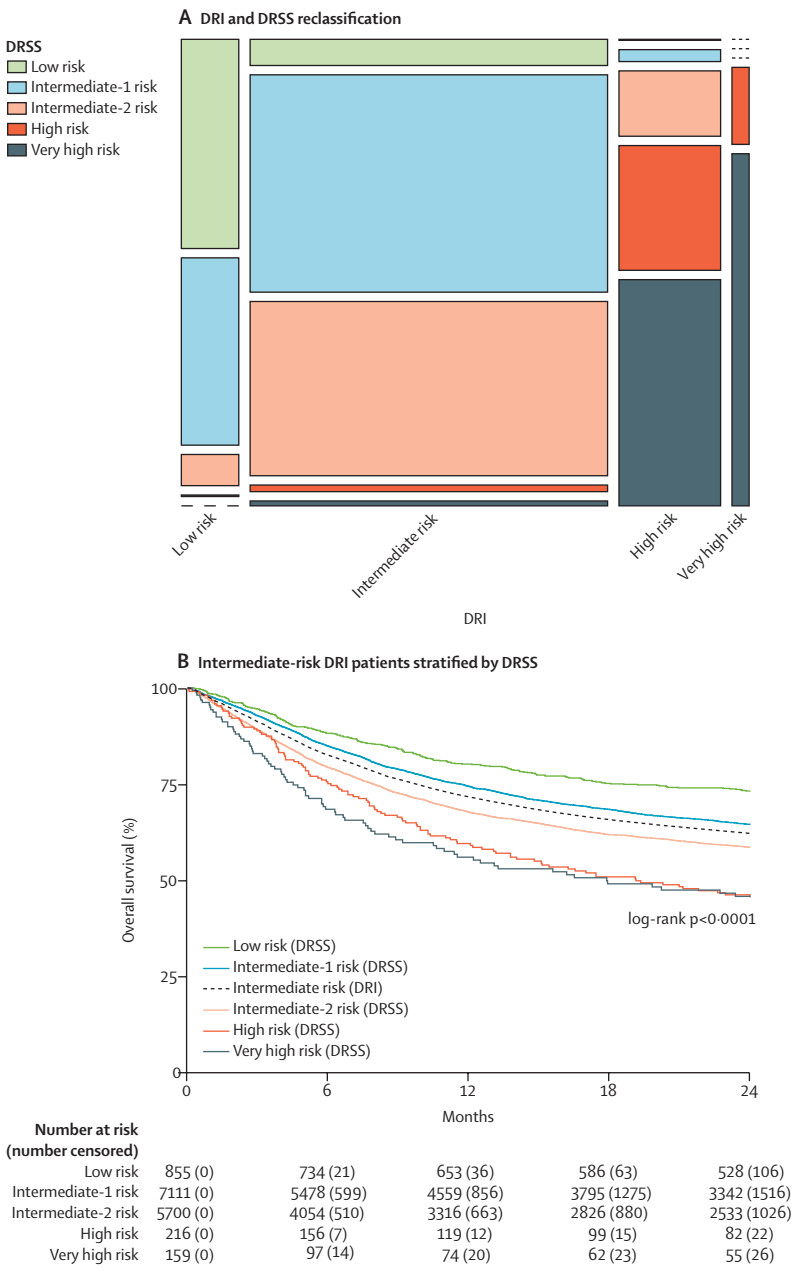

Figure 4: **Reclassification of the DRI intermediate risk group by the DRSS**
A mosaic plot comparing the distribution of risk assignments in the DRSS and revised DRI over the tuning and geographical validation cohorts (A). Column width represents the proportion of DRI categories. Column hight represent the proportion of DRSS categories. Most patients were categorised as intermediate risk by DRI and were further stratified by the DRSS. Overall survival in patients classified by the revised DRI as intermediate risk, in their respective DRSS risk categories (B). DRI=disease-risk index. DRSS=disease-risk stratification system.

separated patients into four distinct risk groups associated with increasing risk of mortality for intermediate-2 risk (HR 1·34 [95% CI 1·04–1·74], p=0·025), high risk (HR 2·03 [95% CI 1·39–2·95], p=0·00023) and very-high risk (HR 2·26 [95% CI 1·62–3·15], p<0·0001) patients compared with the low risk and intermediate-1 risk group (appendix pp 11–12). The condensed scheme corresponded with 66·6% (95% CI 61·6–71·6; low risk and intermediate-1 risk), 55·4% (48·3–62·5; intermediate-2 risk), 40·4% (27·0–53·7; high risk), and 34·8% (23·4–46·3; very high risk) 2-year overall survival (figure 3D). The DRSS remained an independent predictor of mortality after adjusting for ex-vivo CD34$^+$ cell depletion in a sensitivity analysis (appendix p 13).

The DRI has a total of 44 categories versus 55 in the DRSS (appendix p 14). Including only patients who could be classified according to both systems, the AUC for 2-year overall survival with DRSS and DRI in the derivation cohort was 61·0 versus 58·9, 61·6 versus 59·27 in the tuning cohort, 63·3 versus 62·0 in the internal geographic cohort, and 61·6 versus 60·9 in the external cohort. In the derivation set, 709 (2·8%) of 25 534 patients were unclassifiable by the DRI but were captured in the DRSS. In the derivation cohort, the DRI classified 16 510 (65%) of 25 534 patients as intermediate risk; 11 889 (65%) of 18 365 patients as intermediate risk in the tuning cohort, 2152 (64%) of 3366 patients as intermediate risk in the internal geographic validation cohort, and 426 (65%) of 660 patients in the external geographic validation cohort. Corresponding estimates of 2-year overall survival were 62·5% (95% CI: 61·6–63·3; derivation cohort), 61·5% (60·6–62·5; tuning cohort), and 64·8% (62·8–66·9; internal geographical validation and external-validation cohorts). The DRSS reclassified intermediate-risk DRI patients, with 855 (6%) low risk, 7111 (51%) intermediate-1 risk, 5700 (41%) intermediate-2 risk, and 375 (3%) high risk or very high risk of 14041 patients in a subanalysis combining the tuning and internal geographic validation cohorts (figure 4A). In the external-validation cohort 268 (62%) were classified as low risk or intermediate-1 risk and 140 (35%) as intermediate 2 (appendix p 38) of 440 intermediate DRI patients. Across cohorts, the reclassified DRSS tiers within the DRI intermediate-risk group were associated with distinct survival trajectories (figure 4B, appendix p 38). For instance, in the tuning and geographical validation cohort, patients categorised as intermediate-risk DRI had an estimated 2-year overall survival probability of 62·1% (95% CI 61·2–62·9); by DRSS, however, the same group was segregated into the five risk groups with 2-year overall survival of 73·1% (70·1–76·2; low risk), 64·4% (63·2–65·6; intermediate-1 risk), 58·5% (57·1–59·9; intermediate-2 risk), 45·5% (38·7–52·4; high risk) and 45·7% (37·4–54·0; very high risk).

Discussion

Overall survival following allogeneic HSCT is heavily dependent on the histological diagnosis and remission status at the time of transplantation.[2,3] On the basis of these two features and additional molecular and cyto-genetic data, we constructed the DRSS; a novel risk stratification system. The DRSS includes 15 diagnoses with a total of 55 levels grouped into five risk strata. It was

validated in two hold-out datasets; one internal from the EBMT and one external from a single-centre US cohort. Across all populations, the DRSS was the most important determinant of overall survival. Increasing risk of death with each level was primarily driven by relapse, suggesting that disease biology drives classification.

Acute myeloid leukaemia was the leading indication for allogeneic HSCT in this study.[1] In the DRI,[2,3] patients with acute myeloid leukaemia who had a complete remission were grouped without respect to complete remission order. De-novo and secondary acute myeloid leukaemia were considered as a single entity and *FLT3*-ITD and *NPM1* mutation status were not included. Acute myeloid leukaemia categories have been refined in the DRSS. In agreement with Granfeldt Østgård and colleagues,[12] patients with de-novo acute myeloid leukaemia had improved overall survival when compared to patients with secondary acute myeloid leukaemia (appendix p 17). We did not account for secondary acute myeloid leukaemia causes (ie, therapy *vs* antecedent haematological disorder related), which might have further segregated patients.[18] Nevertheless, a distinction between de-novo and secondary acute myeloid leukaemia was informative and was therefore included. De-novo acute myeloid leukaemia was further sub-classified on the basis of the numerical order of remission; transplantation in first complete remission was associated with better survival than in later complete remission. Notably, among patients with intermediate-risk cytogenetics who were in either first complete remission or later complete remission, molecular markers had a major prognostic role. In first complete remission, *FLT3*-ITD^{+} and *NPM1*^{WT} defined a distinct group with inferior survival, while any of the three remaining possible combinations of *FLT3*-ITD and *NPM1* mutation statuses resulted in overlapping survival and were aggregated. The absence of separation between molecular subtypes might reflect selection bias as current guidelines suggest that acute myeloid leukaemia *FLT3*-ITD^{-} and *NPM1*^{mut} should be treated with consolidative chemotherapy.[13] Latent covariates, such as initial induction failure and measurable residual disease (MRD), which are not captured in the registry, could result in an increased risk of recurrence and referral for transplantation in first complete remission. In subsequent complete remission, the sample size did not allow exploration of the role of *NPM1*. *FLT3*-ITD status strongly stratified patients, to the extent that patients with *FLT3*-ITD acute myeloid leukaemia had poor outcomes similar to that observed with adverse-risk cytogenetics (appendix p 17). Therefore, we grouped them into one category. *FLT3*-ITD and *NPM1* mutational status are central determinants of acute myeloid leukaemia therapeutic strategy.[13] Their incorporation to transplantation risk schemes has lagged since standardised reporting to registries has begun since the year 2016. Including these markers in the DRSS reflects a contemporary strategy to assess risk in patients with acute myeloid leukaemia undergoing allogeneic HSCT.

Prognostication in acute lymphoblastic leukaemia is a moving target as practice is evolving. Philadelphia-positive acute lymphoblastic leukaemia, which did not have a distinct prognosis from Philadelphia-negative acute lymphoblastic leukaemia in the revised-DRI,[2,3] was among the entities with the lowest risk for overall mortality in the DRSS. This improvement possibly reflects the routine clinical use of pre-transplantation and post-transplantation tyrosine-kinase inhibitors,[19] which was only partially captured in the registry. Risk estimation in acute lymphoblastic leukaemia will continue to change as more data for MRD and previous therapies accumulate.[20] Progress in the care of other haematological malignancies will change the profile of patients coming into transplantation. Outcomes of transplantation as an advanced treatment line could ultimately be worse than historical controls. In patients with aggressive B-cell non-Hodgkin lymphoma or T-cell non-Hodgkin lymphoma, our findings suggest that achieving a complete remission before transplantation is imperative as patients who were not in a full remission were at high or very-high risk of mortality. Novel targeted therapies offer new hope in these populations.[21,22] Overall, care in lymphoid malignancies is evolving. Therefore, adjustment of transplantation indications and risk assessment will be required in the coming decade.

Risk grouping is inherently linked to loss of prognostic information.[23] Acknowledging this limitation, risk categorisation is clinically useful and facilitates comparative studies across heterogeneous populations. On the derivation set, the large sample size allowed for stratification of patients into five risk groups, which was maintained in the tuning and geographical validation cohorts. The difference in risk between the low and intermediate-1 risk groups was small, albeit statistically significant. In the external validation cohort, the first two levels had an overlapping risk for overall mortality. The difference might have been related to the smaller sample size or major differences between the cohorts' features, namely, the common application of CD34-selected graft in the external cohort, as well as its absence of cord-blood or haploidentical transplants. Importantly, the prognostic utility of DRSS held after adjusting for T cell depletion in the internal and external validation cohorts (appendix pp 9, 13), suggesting that it is platform-independent. Because transplantation studies are often restricted by sample size, as is the case in the external validation cohort, a four-level rather than five-level scheme, merging low risk and intermediate-1 risk groups, could be appropriate in such scenarios.

Prognostic classification is not fixed and should account for emerging data in future studies. The DRSS builds upon the scaffolds of the DRI,[2,3] which has facilitated analyses of heterogeneous cohorts. However, at least 60% of patients in our cohort—and other cohorts[3]—fall under the intermediate risk group with DRI, limiting its utility.[24] The new scheme has more balanced grouping even when

considered as four, rather than five levels. Patients at the extremes could be candidates for strategies aimed at improving disease control (ie, patients who are high risk) or decreasing transplant toxicity (ie, patients who are low risk). The DRSS had a slightly higher AUC than the DRI. However, similar to the DRI, it aims to stratify risk rather than provide an individualised estimate of survival. Therefore, the AUC is not an optimal metric to evaluate both models. Overall, prognostic tools such as the DRI and DRSS provide an estimate of the relative risk and not outcome probabilities. Therefore, they should be used for risk stratification. To provide accurate probabilistic estimates of post-transplantation events, prediction models should be developed on disease-specific cohorts and include granular information regarding patient, disease, and treatment features.

Diagnosis and disease status are among the primary drivers of treatment success.[1–4] As a result, it is a challenge to investigate allogeneic HSCT outcomes because studies often include cohorts with a wide range of indications.[1,25–27] To account for this heterogeneity, we propose the DRSS for estimating the risk of disease-associated mortality. The system was developed on one of the largest cohorts ever used in a transplantation study and was rigorously validated, showing its applicability in the widest range of settings. Nevertheless, the DRSS would benefit from independent validation in additional cohorts with differing practices, disease distribution, and transplant centre experience. Importantly, HSCT prognostication is continuously changing as care of haematological malignancies improves.[1] Therefore, the DRSS should be updated over time as new markers are introduced to registries. Future versions will optimally include a more comprehensive set of molecular and cytogenetic markers and MRD, which is currently not routinely captured in registries.[20,28–30] A similarly constructed system for paediatric transplantation would also be valuable and would necessitate the inclusion of non-malignant transplant indications. We see several applications for the DRSS. First, it can be used to facilitate interpretation and analysis of prospective and retrospective studies, including cohorts with mixed transplant indications. Second, DRSS can serve as a benchmark for transplantation studies and informed consent discussions, as it was developed and tested in nearly 50000 patients. We provide an interactive interface for clinicians and investigators to further explore our findings. Finally, the DRSS promotes the design of non-disease-specific trials (eg, conditioning regimens studies and graft-versus-host disease prophylaxis), opening the door to broader populations.

Contributors

RS, JAF, and AN were responsible for study concept and design. RS, JAF, ML, CC, AB, FB, GB, FC, SC, SGie, MHG, J-EG, SGir, AJ, SM, RJO, EBP, ZP, AR, JS, CSS, BNS, CS, AS, RT, JV, IY-A, MAP, MM, and AN were responsible for acquisition, analysis, and interpretation of data. RS, JAF, and AN were responsible for drafting the manuscript. RS, JAF, ML, CC, AB, FB, GB, FC, SC, J-EG, SGie, MHG, SGir, AJ, SM, RJO, EBP, ZP, AR, JS, CSS, BNS, CS, AS, RT, JV, IY-A, MAP, MM, and AN were responsible for critical revision of the manuscript for important intellectual content. RS and JAF were responsible for statistical analyses. RS, JAF, and ML were responsible for data access and verification of data. ML, CC, MAP, MM, and AN were responsible for administrative, technical, and material support. RS and AN were responsible for study supervision. Authors RS, JF, and ML had full access to all data.

Declaration of interests

FB received travel grants from Celgene, AbbVie, Novartis, Pfizer, and Sanofi, and speaker honoraria from AbbVie. SM serves in a data monitoring committee of Bayer. She received a travel grant from Gilead and a speaker personal fee from Janssen. RJO has received royalties following licensure of the EBV-specific T-cell bank by Atara Biotherapeutics and has subsequently received research support and consultant fees from Atara Biotherapeutics. SGir received research funding from Amgen, Actinuum, Celgene, Johnson & Johnson, Miltenyi, Takeda, and Omeros. He served on the advisory board of Amgen, Actinuum, Celgene, Johnson & Johnson, Janssen, JAZZ Pharmaceutical, Takeda, Novartis, Kite, and Spectrum Pharma. CSS served as a paid consultant on advisory boards for Juno Therapeutics, Sanofi-Genzyme, Spectrum Pharmaceuticals, Novartis, Genmab, Precision Biosciences, Kite, Gilead, Celgene, Bristol Myers Squibb, Gamida Cell, Karyopharm Therapeutics, and GlaxoSmithKline. He has received research funds for clinical trials from Juno Therapeutics, Celgene, Bristol Myers Squibb, Precision Biosciences, and Sanofi-Genzyme. MAP received personal fees from Abbvie, Bellicum, Bristol Meyers Squibb, Celgene, Cidara Theraputics, Incyte, Kite, Gilead, Medigene, Miltenyi, MolMed, Nektar Therapeutics, NexImmune, Novartis, Omeros, Merck, Servier, and Tekeda. He serves in Data Safety and Monitoring Board of Cidara Therapeutics, Medigene, and Servier. He received clinical trial support from Incyte, Kite, Gilead, and Miltenyi. MM received personal fees from Sanofi, Jazz, Amgen, Takeda, Novartis, Janssen, Celgene, Adaptive Biotechnologies, Astella, Pfizer, Stemline, and GlaxoSmithKline. He received grant support from Sanofi, Jazz, and Janssen. All other authors declare no competing interests.

Data sharing

Requests for data can be made through the senior author, Arnon Nagler, at: arnon.nagler@sheba.health.gov.il.

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