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REVIEW

Up-to-date tools for risk assessment before allogeneic hematopoietic cell transplantation

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Cure of malignant and non-malignant hematological diseases is potentially possible after allogeneic hematopoietic stem cell transplantation (HCT). Accurate evaluation of the risk–benefit ratio for an individual patient could improve the decision-making process about transplant, which ultimately would increase the likelihood of success. Several transplant-related models were designed in an effort to optimize decision-making about suitable candidates for allogeneic HCT. In 1998, The European Society for Blood and Marrow Transplantation (EBMT) developed a five-component pretransplantation risk scoring system for patients with CML. The EBMT score was later tested in patients with various hematological disorders, and it was shown to stratify risks of mortality after allogeneic HCT. More recent research efforts focused on models that assess health status before HCT. A HCT-specific comorbidity index was designed to assign weights to 17 relevant comorbidities that were shown to independently predict non-relapse mortality. Performance status scales and comprehensive geriatric assessment tools might uncover additional overall health limitations that affect long-term survival among older recipients of allogeneic HCT. Other models include the pretransplantation assessment of mortality score that summarizes the impacts of eight different pretransplantation patient- and disease-specific variables into a 50-point model that predicts survival. The disease-risk index captures the impact of primary diagnoses and disease status on relapse and survival following allogeneic HCT. The values and limitations of each model are discussed herein. We also provide insight on how to use these models in the clinic to decide about offering allogeneic HCT with the most suitable conditioning regimen intensity.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative treatment for various malignant and non-malignant hematological disorders. The rate of utilization of this treatment modality is unremitting. However, this comes at a price. Allogeneic HCT could lead to significant transplant-related mortality. As a result, decision-making about referral to allogeneic HCT is a challenging task, both for physicians and patients. Therefore, there is a great need for robust tools to help physicians identify which patients should be treated with high-dose conditioning regimens, which are best suited for reduced-intensity conditioning (RIC) regimens, and which patients should not be offered allogeneic HCT.

Currently, there is a number of risk-assessment models that are used by clinicians and investigators. Some of these models use variables of patients' health status, for example, the HCT-specific comorbidity index (HCT-CI),[1] some focus on cancer-related variables, for example, the disease-risk index (DRI),[2] whereas others incorporate a number of patient- and disease-specific risk variables into combined models, for example, the European Society for Blood and Marrow Transplantation (EBMT)[3] and pretransplantation assessment of mortality (PAM)[4] risk scores. Here we discuss (1) the stages of development and validation of the currently available models with emphasis on their relative strengths and potential limitations; (2) the use of these models in an integrated approach to guide decisions about allogeneic HCT; and (3) future directions to improve our abilities to predict HCT outcomes.

PATIENT-SPECIFIC RISK-ASSESSMENT MODELS

HCT-CI

Development. To enhance our ability to evaluate comorbidities before allogeneic HCT, an HCT-CI was developed by modifying another non-transplant index, the Charlson comorbidity index (CCI),[5] in three different ways.[1] First, laboratory data, pulmonary function tests, ejection fraction, and values of bilirubin and hepatic transaminases were introduced into the definitions of pulmonary, cardiac and hepatic comorbidities, respectively. Second, all comorbidities encountered in the studied population of HCT recipients were included in a risk-assessment analysis. New weights were then generated for the impacts of comorbidities on non-relapse mortality (NRM).

The study included 1055 patients with different hematologic diseases who were given allogeneic HCT after nonmyeloablative ($n = 294$) or high-dose ($n = 761$) conditioning regimens. Patients were randomly divided into a training ($n = 708$) and a validation set ($n = 347$). Integer weights of comorbidities were calculated based on adjusted hazard ratios (HRs) from Cox proportional hazard models of NRM. The new HCT-CI included 17 comorbidities acquiring scores from 1 to 3 (Table 1). In the validation set, the HCT-CI scores captured more patients with comorbidities

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Table 1. Definitions of comorbidities included in the HCT-CI and the augmented HCT-CI and their corresponding scores

The HCT-CI		
Comorbidity	*Definition*	*Score*
Arrhythmia	Any type of arrhythmia that has necessitated the delivery of a specific anti-arrhythmia treatment at any time point in the patient's past medical history.	1
Cardiac	Coronary artery disease,[a] congestive heart failure, myocardial infarction or EF $\leqslant$ 50%.	1
Inflammatory bowel disease	Crohn's disease or ulcerative colitis requiring treatment at any time point in patient's past medical history	1
Diabetes	Requiring treatment with insulin or oral hypoglycemic agents continuously for 4 weeks before the start of conditioning.	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident.	1
Psychiatric disturbance	Any disorder requiring continuous treatments for 4 weeks before the start of conditioning.	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5 × ULN or AST/ALT > ULN to 2.5 × ULN; at least two values of each within 2 or 4 weeks before the start of conditioning.	1
Obesity	Patients with a BMI > 35 kg/m^2 for patients > 18 years or a BMI for age of $\geqslant$ 95th percentile for patients of $\leqslant$ 18 years of age.	1
Infection	Requiring antimicrobial treatment starting from before conditioning and continued beyond day 0.	1
Rheumatologic	Requiring specific treatment at any time point in the patient's past medical history.	2
Peptic ulcer	On the basis of prior endoscopic or radiologic diagnosis.	2
Moderate/severe renal	Serum creatinine > 2 mg/dL (at least two values within 2 or 4 weeks before the start of conditioning), on dialysis or prior renal transplantation.	2
Moderate pulmonary	Corrected DLco (via Dinakara equation) and/or FEV1 of 66-80% or dyspnea on slight activity.	2
Prior malignancy	Treated at any time point in the patient's past history, excluding non-melanoma skin cancer.	3
Heart valve disease	Of at least moderate severity, prosthetic valve or symptomatic mitral valve prolapse as detected by echocardiogram.	3
Severe pulmonary	Corrected DLco (via Dinakara equation) and/or FEV1 $\leqslant$ 65% or dyspnea at rest or requiring oxygen.	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin > 1.5 × ULN or AST/ALT > 2.5 × ULN; at least two values of each within 2 or 4 weeks before the start of conditioning.	3
Augmented HCT-CI: all of the above plus		
High ferritin	Values of $\geqslant$ 2500 as measured the closest before the start of conditioning.	1
Mild hypoalbuminemia	Values of < 3.5–3.0 as measured the closest before the start of conditioning.	1
Thrombocytopenia	Values of < 100 000 as measured the closest before the start of conditioning.	1
Moderate hypoalbuminemia	Values of < 3.0 as measured the closest before the start of conditioning.	2

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; DLco = diffusion capacity of carbon monoxide; EF = ejection fraction; FEV1 = forced expiratory volume in 1 s; HCT-CI = hematopoietic stem cell transplantation-specific comorbidity index; ULN = upper limit of normal. [a]One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft.

compared with the CCI. HCT-CI scores of 1–2 and $\geqslant$3 were found in 34% and 28% of patients, whereas only 10% and 3% of patients had CCI scores of 1 and $\geqslant$2, respectively. HCT-CI scores of 0, 1–2 and $\geqslant$3 predicted NRM incidences of 14%, 21% and 41%, respectively, and survival rates of 71%, 60% and 34%, respectively (Figure 1). The HCT-CI scores showed higher discriminative power than the CCI scores both for NRM (*c*-statistic estimate of 0.692 versus 0.546, $P < 0.001$) and survival (*c*-statistic estimate of 0.661 versus 0.561, $P < 0.001$), respectively.

Validation. The HCT-CI score has been extensively validated in several retrospective and prospective multi-center studies. Some of these studies were performed in large data sets with various hematological disorders,[6–8] whereas others were performed in single disease series.[9–11] Overall, 25 studies could prove the validity of HCT-CI score as an independent predictor of outcomes. Results of these studies are summarized in Table 2.[6–30] All of these studies used NRM and overall survival (OS) as the outcomes of interest to validate the index. In addition, five studies utilized concordance probability estimates, such as *c*-statistic index, to measure the discriminative power of the HCT-CI.[7,8,11,20,29] On the other hand, only eight studies found the HCT-CI not to provide prognostic information due to several reasons that are discussed under the section 'Limitations'.[31–38]

Advantages. The HCT-CI summarizes the impact of relevant comorbidities on HCT outcomes into an unified model. The index contains objective laboratory data to define certain comorbidities, allowing for more accurate measurement of comorbidities burden compared with non-transplant-specific indices.

The index could potentially be used to guide selection of conditioning regimens. For example, HCT-CI scores of >3 were used as a stratification criterion to randomize patients with myelodysplastic syndromes (MDS) or AML between receiving high-dose versus RIC regimens before allogeneic HCT (NCT00322101).

The HCT-CI was also used in retrospective studies to guide decision-making before allogeneic HCT for a given hematologic malignancy as detailed in Table 3.

In addition, the HCT-CI score could predict risks of development of certain post-transplant complications. A recent analysis of data from 2985 allogeneic HCT recipients form five different US institutions demonstrated a strong association between higher HCT-CI scores and development of grades III and IV acute GvHD (Table 4), and subsequent mortality following diagnosis of grade II (HR = 1.24; $P < 0.0001$) or grades III and IV acute GvHD (HR = 1.19; $P < 0.0001$).[39] In another study of 1775 adult survivors 3–18 years after allogeneic HCT, higher pretransplant HCT-CI scores were associated with impaired physical health, increased depression, increased distress and diminished social support among long-term survivors.[40] Thus, the HCT-CI can be used to guide intervention studies aimed at improving the quality of life among long-term survivors.

The index can best be used in combination with other variables covering other patient- and disease-specific risks (Table 5):

- A composite HCT-CI score and Karnofsky performance status[14]
- A combined comorbidity/relapse model[41]
- A composite HCT-CI score and EBMT risk score[42]

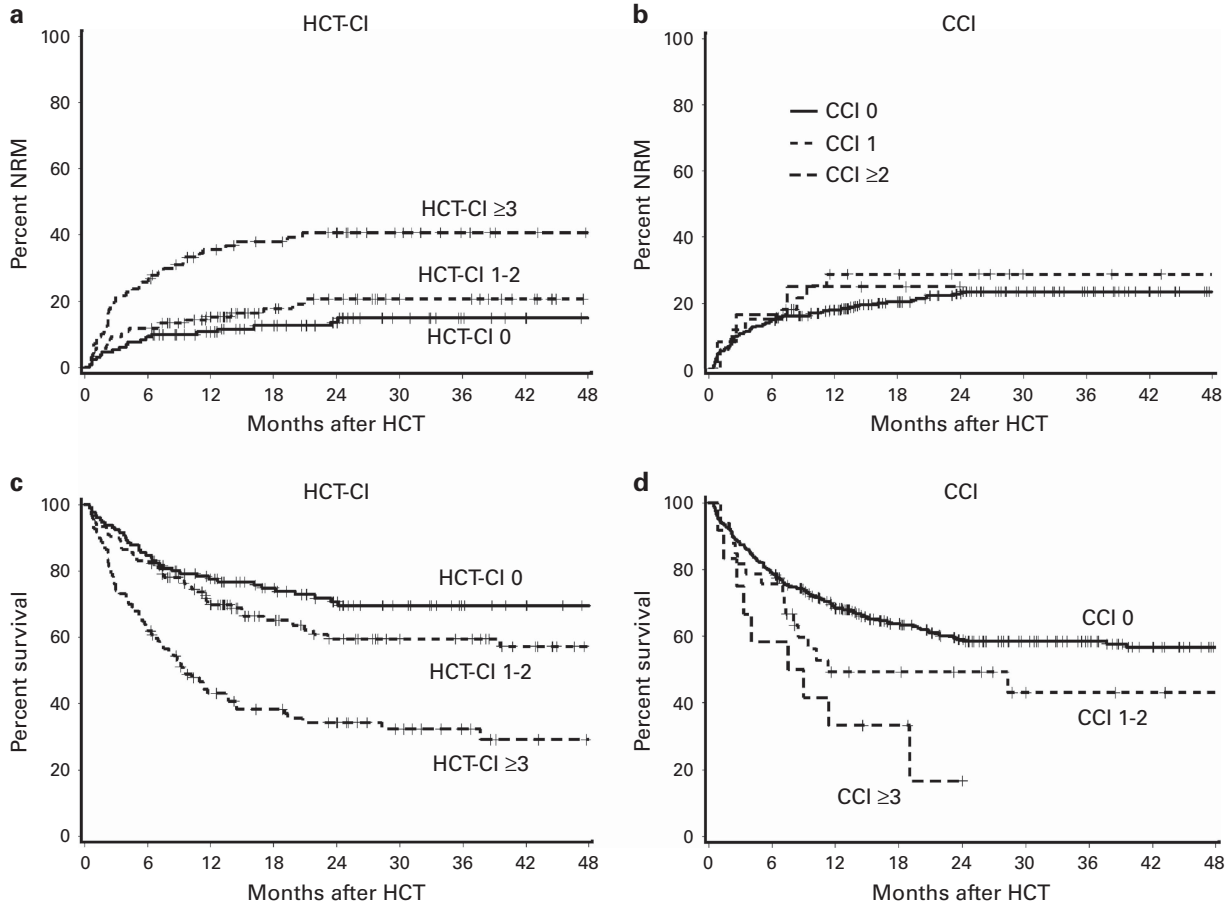

Figure 1. The HCT-CI compared with CCI. Cumulative incidence of NRM as stratified by (**a**) HCT-CI compared with (**b**) the original CCI and Kaplan–Meier estimates of survival as stratified by (**c**) the HCT-CI compared with (**d**) the original CCI. CCI = Charlson comorbidity index; HCT-CI = hematopoietic cell transplantation-specific comorbidity index; NRM = non-relapse mortality. This research was originally published in *Blood*, Sorror *et al.*[1] © American Society of Hematology.

- A combined HCT-CI score and the instrumental activities of daily living (IADL) for HCT recipients of 50 years of age or older.[43]

Limitations. Although 25 out of 33 studies proved the discriminative validity of the HCT-CI, eight studies did not (Table 2).[31–38] Limited sample size was evident in most of the disagreeing studies. Lack of full agreement on the validity of the index was thought to limit its worldwide applicability. However, in two recent large prospective studies, the HCT-CI was shown to predict both NRM and OS after allogeneic HCT given to patients in Italy or United States.[6,8] Another large retrospective study showed the index to be a valid prognostic factor across different conditioning regimens, ages and centers.[7] In the latter study, investigators calculated a sample size of at least 200 patients to be required for appropriate validation of the HCT-CI.

Another potential limitation of the index was the weak agreement on comorbidity coding by evaluators at different institutions.[34] To ensure accuracy and consistency of comorbidity coding among investigators, a systematic methodology for reviewing medical charts (Figure 2) and consistent guidelines for comorbidity coding were summarized in a web-based calculator (www.hctci.org).[44] This brief training program resulted in improvement of inter-rater reliability among different evaluators from 0.433 to >0.90 as measured by weighted kappa statistic estimates.

Some studies did not show differences in outcomes among patients with scores 0, 1 and 2, suggesting that the HCT-CI only performs as a binary categorizer.[20] The definitions of low, intermediate and high risks for HCT-CI are meant to be relative and not absolute categorizations, as the increasing scores of the HCT-CI were meant to capture a general trend for increases in risks of NRM. The range of these increases would differ based on the intensity of transplant conditioning, disease status and other factors. For example, patients with scores of 1–2 could have comparable NRM with patients with scores of 0 if they are given a reduced-intensity regimen, but higher NRM if the conditioning regimen is higher in intensity. Therefore, the best way to define HCT-CI risk groups would probably rely on stratifying patients into roughly equally distributed subgroups. Alternatively, HCT-CI scores could be employed in multivariate models as a continuous variable.

There have been questions whether exact instead of integer weights of comorbidities would improve the model performance or whether new weights need to be developed for different transplant settings. One study looked at recalibrating the relative scores of the individual components of the HCT-CI by replacing the integer weights, with the exact HRs of different comorbidities. Authors concluded that six comorbidities are no longer contributing to the total score.[12] However, these results could not be validated in a separate independent cohort. In fact, the HCT-CI score in its original structure was superior to the modified index in prognostication of NRM and survival.[45]

Table 2. Performance of the HCT-CI as a prognostic factor in single and multi-center; retrospective and prospective studies

Study	*Number of patients*	*Types of donors*	*Types of conditioning intensity*	*Outcomes*		*Comments*	*Statistical Methods used for validation*		
				Predicted by the HCT-CI	*Not predicted by the HCT-CI*		*Rates*	*Multivariate HRs*	*C-statistic estimates*
Kerbauy *et al.*[13]	43	HLA matched ($n=35$) HLA-MM ($n=8$)	MA ($n=37$) NMA ($n=6$)	4-year NRM and OS	—	Small sample size. Diagnosis: chronic myelomonocytic leukemia.	√	—	—
Maruyama *et al.*[9]	132	Related ($n=70$) Unrelated ($n=62$)	MA ($n=52$) RIC ($n=80$)	2-year NRM and OS in MA patients	2-year NRM and OS in RIC patients	Diagnoses: leukemia/lymphoma in nonremission.	√	√	—
Kerbauy *et al.*[10]	104	Related ($n=58$) Unrelated ($n=45$)	MA ($n=95$) NMA ($n=9$)	5-year NRM and OS	—	Diagnoses: idiopathic myelofibrosis, advanced polycythemia vera and essential thrombocythemia.	√	√	—
Sorror *et al.*[11]	244	HLA matched ($n=220$) HLA-MM ($n=24$)	MA ($n=202$) NMA ($n=18$) RIC ($n=24$)	2-year NRM and OS	—	Diagnosis: AML in 1st CR.	√	√	√
Sorror *et al.*[30]	577	HLA matched ($n=523$) HLA-MM ($n=54$)	MA ($n=425$) NMA ($n=125$)	2-year NRM and OS	—	Adding disease status improved prediction. Diagnosis: AML/MDS.	√	√	—
Sorror *et al.*[14]	341	Related ($n=160$) Unrelated ($n=181$)	NMA ($n=341$)	2-year NRM and OS	—	Adding KPS improved prediction Diagnosis: malignant and benign hematological disorders.	√	√	—
Artz *et al.*[15]	112	HLA matched ($n=103$) HLA-MM ($n=9$)	RIC	1-year OS	1-year NRM	Small sample size. Diagnosis: malignant and benign hematological disorders.	√	√	—
Sorror *et al.*[16]	220	HLA matched ($n=205$) HLA-MM ($n=15$)	MA ($n=68$) NMA ($n=152$)	3-year NRM and OS	—	Diagnoses: chronic lymphocytic leukemia and lymphoma.	√	√	—
Xhaard *et al.*[31]	286	Related ($n=149$) Unrelated ($n=63$) Other ($n=74$)	MA ($n=167$) NMA ($n=119$)	—	2-year NRM and OS	Lack of information on PFT. Diagnosis: malignant and benign hematological disorders.	√	√	√
Majhail *et al.*[12]	373	HLA matched ($n=184$) UCB ($n=189$)	MA ($n=150$) NMA ($n=223$)	2-year NRM and OS in overall cohort	2-year NRM and OS in subgroup analysis	Small number of patients in subgroups Diagnosis: malignant and benign hematological disorders.	√	√	—
Farina *et al.*[17]	203	Related ($n=121$) Unrelated ($n=82$)	RIC ($n=154$) NMA ($n=49$)	2-year NRM,OS and PFS,	—	Diagnosis Lymphoma and myeloma.	√	√	—
Guilfoyle *et al.*[37]	187	Related ($n=138$) Unrelated ($n=49$)	MA ($n=177$) NMA ($n=10$)	—	2-year NRM and OS	(1) High incidence of pulmonary comorbidities (2) Small sample size (3) Data collected from 1990–2005 (significant heterogeneity in treatment protocols and supportive care). Diagnosis: malignant and benign hematological disorders.	√	√	—
Kataoka *et al.*[18]	187	HLA matched ($n=143$) HLA-MM ($n=44$)	MA ($n=170$) NMA ($n=17$)	(1) 3-year NRM and OS (2) OS in low-risk disease subgroup	OS in high-risk disease subgroup	Small number of patients in subgroups. Diagnosis: malignant and benign hematological disorders.	√	√	—
Lim *et al.*[19]	128	HLA matched ($n=94$) HLA-MM ($n=34$)	RIC	3-year NRM, OS and DFS	—	Diagnosis: AML/MDS.	√	√	—
Barba *et al.*[20]	194		RIC	2-year NRM and OS	—	Diagnosis: malignant and benign hematological disorders.	√	√	√

Table 2. (Continued)

Study	Number of patients	Types of donors	Types of conditioning intensity	Outcomes		Comments	Statistical Methods used for validation		
				Predicted by the HCT-CI	Not predicted by the HCT-CI		Rates	Multivariate HRs	C-statistic estimates
		Related ($n=153$) Unrelated or MM ($n=41$)							
Terwey *et al.*[32]	151	HLA matched ($n=134$) HLA-MM ($n=17$)	MA ($n=138$) RIC ($n=13$)	—	2-year NRM and OS	High frequency of intermediate and high-risk patients (71%). Diagnosis: ALL.	√	√	—
DeFor *et al.*[33]	444	HLA matched ($n=211$) UCB ($n=233$)	MA ($n=169$) NMA ($n=275$)	—	2-year NRM and OS	Using exact HRs rather integer weights of comorbidities for scores calculation.	√	√	√
Birninger *et al.*[34]	340	Related ($n=116$) Other ($n=224$)	MA ($n=133$) NMA ($n=207$)	—	3-year NRM and OS	(1) Unbalanced score categories (2) Possible over-scoring of some comorbidities Diagnosis: high-risk AML.	√	√	—
Smith *et al.*[21]	252	HLA matched ($n=149$) HLA-MM ($n=55$) UCB ($n=48$)	MA ($n=189$) RIC/ NMA ($n=61$) None ($n=2$)	1-year NRM and OS	—	Pediatric population based study Diagnosis: malignant and benign hematological disorders.	√	√	—
Castagna *et al.*[35]	63	HLA matched ($n=59$) HLA-MM ($n=2$) UCB ($n=2$)	RIC	—	1-year TRM and 2-year OS	Small sample size, patients >60 years. Diagnosis: malignant and benign hematological disorders.	√	—	—
Williams *et al.*[36]	96	Related ($n=34$) Unrelated ($n=62$)	MA ($n=33$) RIC ($n=63$)	—	1-year NRM and OS	Small-sized heterogeneous sample. Diagnosis: malignant and benign hematological disorders.	√	√	—
Bokhari *et al.*[22]	121	Related ($n=57$) Unrelated ($n=64$)	RIC	2-year NRM and OS when combined with age and disease status	2-year NRM and OS	Diagnosis: AML/MDS.	√	√	—
Raimondi *et al.*[8]	1937	Related ($n=958$) Unrelated ($n=979$)	MA ($n=1083$) RIC ($n=854$)	2-year NRM and OS	—	A large multi-center prospective study. Diagnosis: malignant and benign hematological disorders.	√	√	√
Mo *et al.*[23]	526	PMRD	MA	2-year NRM, OS and relapse risk	—	Diagnosis: malignant and benign hematological disorders.	√	√	—
Le *et al.*[24]	79	HLA matched	MA	5-year NRM and OS	—	Diagnosis: malignant and benign hematological disorders.	√	√	—
Ratan *et al.*[25]	218	HLA matched and other	MA	5-year NRM,OS and RFS	—	Diagnosis: AML/MDS.	√	√	—
Hashmi *et al.*,[26]	103	Related ($n=45$) Unrelated ($n=58$)	RIC	1-year OS	—	Diagnosis: malignant and benign hematological disorders.	√	√	—
Bayraktar *et al.*[27]	377	HLA matched ($n=277$) HLA-MM ($n=100$)	MA ($n=199$) NMA ($n=178$)	Mortality and 1-year OS in patients admitted to ICU	—	Diagnosis: patients admitted to ICU post allo-HCT.	√	√	—
Chemnitz *et al.*[28]	245	Related ($n=87$) Unrelated ($n=158$)	MA/RIC ($n=167$) NMA ($n=35$) Other ($n=43$)	5-year NRM and OS	—	Diagnosis: malignant and benign hematological disorders.	√	√	—
Nakaya *et al.*[38]	243	Related ($n=68$) Unrelated ($n=175$)	MA ($n=166$) RIC ($n=77$)	—	2-year NRM and OS	A multi-center prospective study. Diagnosis: malignant and benign hematological disorders. HCT-CI was predictive of 2-year NRM and OS using new cutoffs for risk groups (low risk for scores of 0–3 and high risk for scores ⩾4).	√	√	—

Table 2. (Continued)

Study	Number of patients	Types of donors	Types of conditioning intensity	Outcomes		Comments	Statistical Methods used for validation		
				Predicted by the HCT-CI	Not predicted by the HCT-CI		Rates	Multivariate HRs	C-statistic estimates
Elsawy *et al.*[29]	492	HLA-MM ($n=254$) UCB ($n=238$)	MA ($n=308$) NMA/ RIC ($n=184$)	2-year NRM and OS	—	The HCT-CI scores could be used to optimize graft source selection for patients with no suitable matched donors. Diagnosis: malignant and benign hematological disorders.	√	√	√
Sorror *et al.*[6]	19 767	Related (19%) Unrelated (23%) Autologous (58%)	[a]MA (67%) [a]NMA/ RIC (33%)	1 and 3-year NRM and OS	—	A large multi-center prospective study. Diagnosis: malignant and benign hematological disorders.	√	√	—
Elsawy *et al.*[7]	2523	Related (56%) Unrelated (44%)	MA (62%) RIC (18%) NMA (20%)	2-year NRM and OS	—	Diagnosis: malignant and benign hematological disorders.	√	√	√

Abbreviations: DFS = disease-free survival; HCT-CI = hematopoietic cell transplantation-specific comorbidity index; HRs = hazard ratios; ICU = intensive care unit; KPS = Karnofsky performance status; MA = myeloablative; MDS = myelodysplastic syndromes; MM = mismatched; NMA = nonmyeloablative; NRM = non-relapse mortality; OS = overall survival; PFTs = pulmonary function tests; PMRD = partially matched related donor; RFS = relapse-free survival; RIC = reduced-intensity conditioning; TRM = transplant-related mortality; UCB = umbilical cord blood. [a]Recipients of allogeneic HCT.

Modifications. Two recent modifications were introduced to the HCT-CI to improve its discriminative power. In a study of 3033 recipients of allogeneic HCT, who were randomly divided into a training set ($n=1853$) and a validation set ($n=1180$), an age of $\geqslant 40$ years was found to have an impact on NRM that is equivalent to a single comorbidity with a score of 1. A score of 1 was assigned to age of $\geqslant 40$ years to form a composite comorbidity/age index. In the validation cohort, the composite model had a statistically significant higher discriminative capacity for NRM (*c*-statistic estimates of 0.664 versus 0.556; $P<0.001$) and survival (*c*-statistic estimates of 0.682 versus 0.560; $P<0.001$) compared with age alone, respectively. In the same validation cohort, the composite comorbidity/age index stratified patients according to outcomes into four distinct groups compared with three groups for the HCT-CI.[46]

In another study, weights were developed for low albumin, low platelets and high ferritin values. Adding scores for these laboratory values to the HCT-CI resulted in an augmented index that possessed higher *c*-statistic estimate for predicting NRM compared with the HCT-CI alone ($P=0.0007$).[47]

CGA

Use in HCT Recipients. The prognostic role of Comprehensive Geriatric Assesment (CGA) has been shown in patients treated with chemotherapy.[48,49] However, the feasibility of CGA in the setting of HCT is yet to be better defined.

In a single institution prospective study, investigators explored the prognostic role of CGA in 203 patients with ages between 50 and 73 years (median age = 58 years), who received allogeneic HCT for various hematological disorders.[43] In multivariate analysis, the authors identified IADL, slow gait, high HCT-CI scores, low mental health by short-form 36 medical component summary and elevated CRP blood levels to be associated with significantly worse OS. IADL limitation was the most predictive factor of OS (HR = 2.28; $P<0.001$) among all CGA domains. This impact was even more noticeable among patients of >60 years of age (HR = 3.25; $P<0.001$). The authors then combined IADL with the HCT-CI in a single three-point model (Table 5). None of the patients aged $\geqslant 60$ years with a combined score of 2 survived >2 years.[43]

Another prospective study reached a different conclusion. In a group of 126 patients with newly diagnosed AML given allogeneic HCT (median age = 74 years, range 60–90), investigators explored the impact of CGA domains on OS. After adjusting for age and cytogenetic risks in multivariate models, only self-reported cardiac history was an independent prognostic factor for survival (HR = 2.290), whereas the remaining CGA tools were not.[50] Clearly, we need more discovery and validation studies before CGA is introduced in transplant clinics.

Advantages. The use of a shortened and relevant GCA battery might reveal additional vulnerabilities to those captured by comorbidities or performance status that are specific to older patients. Therefore, CGA could further refine pre-HCT risk assessment when considered with other risk factors. Geriatric health limitations might be potentially modifiable in the peri-transplant period to improve HCT outcomes.

Limitations. The use of CGA in the setting of allogeneic HCT is hampered by a number of limitations. A full CGA is probably time-consuming, particularly for sick patients. Some of these patients might not be able to complete the assessment. The assessment could also be time-consuming for the medical staff. A considerable amount of learning needs to be done to encourage patients and physicians on the use of GA models. Moreover, identifying the most relevant components of CGA would further simplify its usage. This is particularly true for the functional components that are uniquely assessed by the CGA. For example, in an analysis of

Table 3. Role of HCT-CI scores in optimizing treatment selection for specific hematological disorders

Study	*Number of patients*	*Disease category*	*Conditioning intensity*	*Risk stratification*						*Comments*
Sorror *et al.*[30]	577	AML ($n=391$) MDS ($n=186$)	MA ($n=452$) NMA ($n=125$)	HCT-CI score	Disease risk	2-yr NRM and OS (%) MA		NMA		Increasing HCT-CI scores and higher disease risk were the two most predictors of mortality. Thus, combined HCT-CI score and disease-risk status stratified patients into 4 groups with distinct outcomes. Patients with HCT-CI scores = 0–2 had comparable risks of 2-year NRM, following high-dose or nonmyeloablative conditioning regimens regardless of their disease status, suggesting their suitability for prospective randomized studies comparing both regimens. On the other hand, those with HCT-CI scores ⩾3 and high-risk diseases experienced higher rates of NRM, but similar survival following high-dose versus nonmyeloablative conditioning regimens, respectively. Novel conditioning regimens with some anti-tumor effect, but potentially tolerable toxicity profile could be explored in this group of patients to improve their survival.[82]
						NRM	OS	NRM	OS	
				0–2	Low	11	78	4	70	
				0–2	Intermediate and high	24	51	3	57	
				⩾3	Low	32	45	27	41	
				⩾3	Intermediate and high	46	24	29	29	
Sorror *et al.*[83]	82	CLL	2-Gy TBI ($n=13$) 2-Gy TBI+fludarabine ($n=69$)	HCT-CI score	LN size	5-yr OS (%)				Combined HCT-CI scores and LN size were the two most predictive factors of outcomes.
				0	< 5 cm	78				
				0	⩾5 cm	43				
				⩾1	< 5 cm	60				
				⩾1	⩾5 cm	27				
Sorror *et al.*[16]	220	CLL and lymphoma	MA ($n=68$) NMA ($n=152$)	HCT-CI score	Conditioning intensity	3-yr NRM (%)	3-yr OS (%)			Patients with HCT-CI score = 0 had no statistically significant differences in outcomes, whereas patients with HCT-CI scores ⩾1 had statistically significant better outcomes with NMA versus MA conditioning regimens, respectively.
				0	NMA	18	68			
				0	MA	15	60			
				⩾1	NMA	28	47			
				⩾1	MA	50	35			
Pavlu *et al.*[84]	271	Imatinib-resistant CML	MA	HCT-CI score	5-yr NRM (%)	5-year OS (%)				CML patients with low HCT-CI scores and low CRP values are better candidates for early MA HCT after imatinib failure.
				0	5.3	69.6				
				⩾1	18.5	55.5				
				CRP (mL/L)	5-yr OS (%)					
				⩽9	70					
				>9	40					

Abbreviations: HCT-CI = hematopoietic cell transplantation-specific comorbidity index; LN = lymph node; MA = myelobalative; MDS = myelodysplastic syndromes; NMA = nonmyeloablative; NRM = non-relapse mortality; OS = overall survival; yr = year.

data from nine studies enrolling a total of 34 485 adults aged 65 years or older, a walk test as a measure of gait speed has been shown to be associated with outcome of elderly patients.[51] In a more recent study, a six-minute walking test (MWT) and a hand grip strength (HGS) test were the best predictors of mortality among 310 hospitalized patients >60 years.[52] In a prospective study, analyzing data from 2273 visits of allogeneic HCT recipients diagnosed with chronic GvHD, both the 2MWT and HGS were significantly associated with global chronic GvHD severity. In multivariable analysis, 2MWT was significantly associated with OS, NRM and failure-free survival; meanwhile no association was observed for HGS.[53] Well-designed and appropriately powered studies are still needed to identify the additional magnitude of prognostic value that some unique CGA components could add to currently used models such as the HCT-CI or Karnofsky performance status. One study is evaluating these components prospectively to determine feasibility of allogeneic HCT and compare its outcomes to those after non-transplant therapies in patients with AML (NCT01929408).

Table 4. Association between HCT-CI scores and development of acute GvHD

HCT-CI score	*Incidence of grades III-IV acute GVHD**
0	13%
1–4	18%
⩾5	24%

*$P < 0.0001$.

DISEASE-SPECIFIC RISK-ASSESSMENT MODELS

DRI

Development. The underlying primary hematologic disease and its response to initial chemotherapy are major determinants of outcomes following allogeneic HCT.[54–56] Investigators from the Dana Farber Cancer Institute and Fred Hutchinson Cancer Research Center (FHCRC) designed a study to develop and validate a novel and comprehensive model that captures the impact of primary diagnosis, disease status, histologic subtypes (for lymphomas)[56–58] and chromosomal aberrations (for AML, ALL and MDS[59,60]) on outcomes. The study included a group of 1539 consecutive patients, who received their first allogeneic HCT between 2000 and 2009 after nonmyeloablative/RIC ($n = 727$) or high-dose ($n = 812$) conditioning regimens.[2] The DRI was derived from Cox proportional hazards models with OS as the main outcome of interest for each diagnosis and disease status. The DRI comprises three disease grouping categories and two status grouping categories resulting in six possibilities of diagnosis/

Table 5. Augmentation of HCT-CI predictability by combining with other models[85]

Composite model	*Risk groups*		*Outcomes at 2 years*		*Outcomes at 4 or 5 years*	
	HCT-CI	*KPS*	*NRM (%)*	*OS (%)*	*NRM (%)*	*OS (%)*
Comorbidity/PS[14]	0–2	>80%	16	68		
	0–2	⩽80%	17	58		
	⩾3	>80%	30	41		
	⩾3	⩽80%	39	32		
Comorbidity/age score[46] (nonmyeloablative versus RIC)	HCT-CI/age					
	0		5–12	81–87		
	1–2		9–18	66–67		
	3–4		17–36	47–54		
	⩾5		35–41	34–35		
Comorbidity/relapse score (patients ⩾60 years old)[41]	HCT-CI	Relapse risk score				
	0	Low				69
	0	Standard				45
	0	High				41
	1–2	Low				56
	1–2	Standard				44
	1–2	High				15
	⩾3	Low				56
	⩾3	Standard				23
	⩾3	High				23
HCT-CI/EBMT[42]	HCT-CI	EBMT				
	0	<4			11	72
	0	⩾4			19	61
	1–2	<4			16	63
	1–2	⩾4			28	48
	⩾3	<4			31	40
	⩾3	⩾4			41	30
HCT-CI/IADL[43]	*Scores*					
HCT-CI score of ⩾3 or IADL score <14 acquire a score of 1. Both abnormalities get a score of 2	0			62		
	1			44		
	2			13		

Abbreviations: EBMT = European bone marrow transplant; HCT-CI = hematopoietic cell transplantation comorbidity index; IADL = instrumental activities of daily living; KPS = Karnofsky performance status; NRM = non-relapse mortality; OS = overall survival; PS = performance status. This research was originally published in ASH Educational Book, Sorror and Estey[85] © American Society of Hematology.

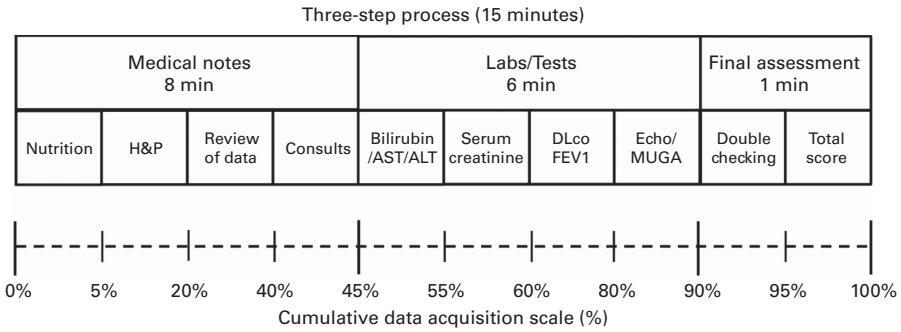

Figure 2. Three-step methodology for comorbidity coding. This research was originally published in *Blood*, Sorror.[44] © American Society of Hematology.

disease status combinations that were collapsed into four risk groups. The DRI predicted excellent 4-year OS and PFS rates of 64% and 56%, respectively, for patients with low-risk, these figures were 6% and 6%, respectively, among very high-risk patients (Table 6 and Figure 3).

The investigators then validated the DRI in an independent cohort of 672 patients from FHCRC. The DRI could successfully stratify rates of OS and PFS among patients in the validation cohort ($P < 0.001$ for both; Figure 4).

Validation. Recently, DRI was further refined and validated in a large study from the Center for International Blood and Marrow Transplant Research comprising 13 131 patients given allogeneic HCT between 2000 and 2010, following nonmyeloablative/RIC (47%) or high-dose (53%) conditioning regimens. Four risk categories were identified with 2-year OS ranging from 64 to 24% ($P < 0.001$) for low- and very high-risk categories, respectively.[61] The authors then attempted to further refine the DRI categories as described under the section 'Modification' below.

Three independent groups of investigators recently tested the discriminative validity of the DRI in their own patient cohorts. Results are summarized in Table 7.

Advantages. DRI provides a uniform model to measure the impacts of various diagnoses/disease status/cytogenetic combinations on survivals, following allogeneic HCT. The DRI index can prove to be a useful tool to compare or adjust results of studies that include heterogeneous hematological diseases. In addition, the index can be useful in comparing outcomes across different transplant centers that treat different diagnoses.

Limitations. DRI lacks essential data on molecular markers of some diseases, for example, FMS-like tyrosine kinase 3 (FLT3) internal tandem duplication status for AML.

As the DRI was developed from a large pool of various diagnoses and disease status, it is possible that the current categories of the DRI might not stratify risks of mortality well within a single disease. Like any other prognostic model, the use of the DRI has to be introduced in appropriately powered studies with sufficient follow-up durations. In a recent study, the DRI was found to stratify risks only in samples of >50 patients with >40 months of follow-up duration.[62] Additional refinements of the DRI might change these parameters.

Modifications. The original developers of the model attempted to modify it in a large Center for International Blood and Marrow Transplant Research study.[61] Changes included the following: (1) patients given RIC or high-dose regimens in 2nd or subsequent PR were grouped together in the low risk category; (2) rare diseases such as Burkitt lymphoma were added; and (3) some disease status combinations were assigned different risk groups than those in the original DRI based on the similarities in outcomes (Table 8). The refined DRI had *c*-statistic estimate of 0.643 for prediction of OS compared with 0.637 for the original DRI; no *P*-value was reported to allow for better quantification of the magnitude of this change.

Table 6. Disease risk index[2,61]

Disease	*Disease risk*
AML favorable cytogenetics	Low
CLL	
CML	
Indolent B-cell NHL	
ALL	Intermediate
AML intermediate cytogenetics	
MDS intermediate cytogenetics	
MPN	
Multiple myeloma	
HL	
DLBCL/transformed indolent B-cell NHL	
Mantle cell lymphoma	
T-cell lymphoma, nodal	
AML adverse cytogenetics	High
MDS adverse cytogenetics	
T-cell lymphoma, extranodal	
Stage	*Stage risk*
Any CR	Low
1st PR	
Untreated	
Chronic phase CML	
2nd or subsequent PR (if RIC)	
2nd or subsequent PR (if MAC)	High
Induction failure	
Active relapse	
Accelerated or blast phase CML	

Overall assignment

Disease risk	*Stage risk*	*DRI*
Low	Low	Low
Low	High	Intermediate
Intermediate	Low	
Intermediate	High	High
High	Low	
High	High	Very high

Abbreviations: DLBCL = diffuse large B-cell lymphoma; HL = Hodgkin lymphoma; MAC = myeloablative conditioning; MDS = myelodysplastic syndromes; MPN = myeloproliferative neoplasms; NHL = non-Hodgkin lymphoma; RIC = reduced-intensity conditioning. This research was originally published in Blood. Armand *et al.*[2] © American Society of Hematology.

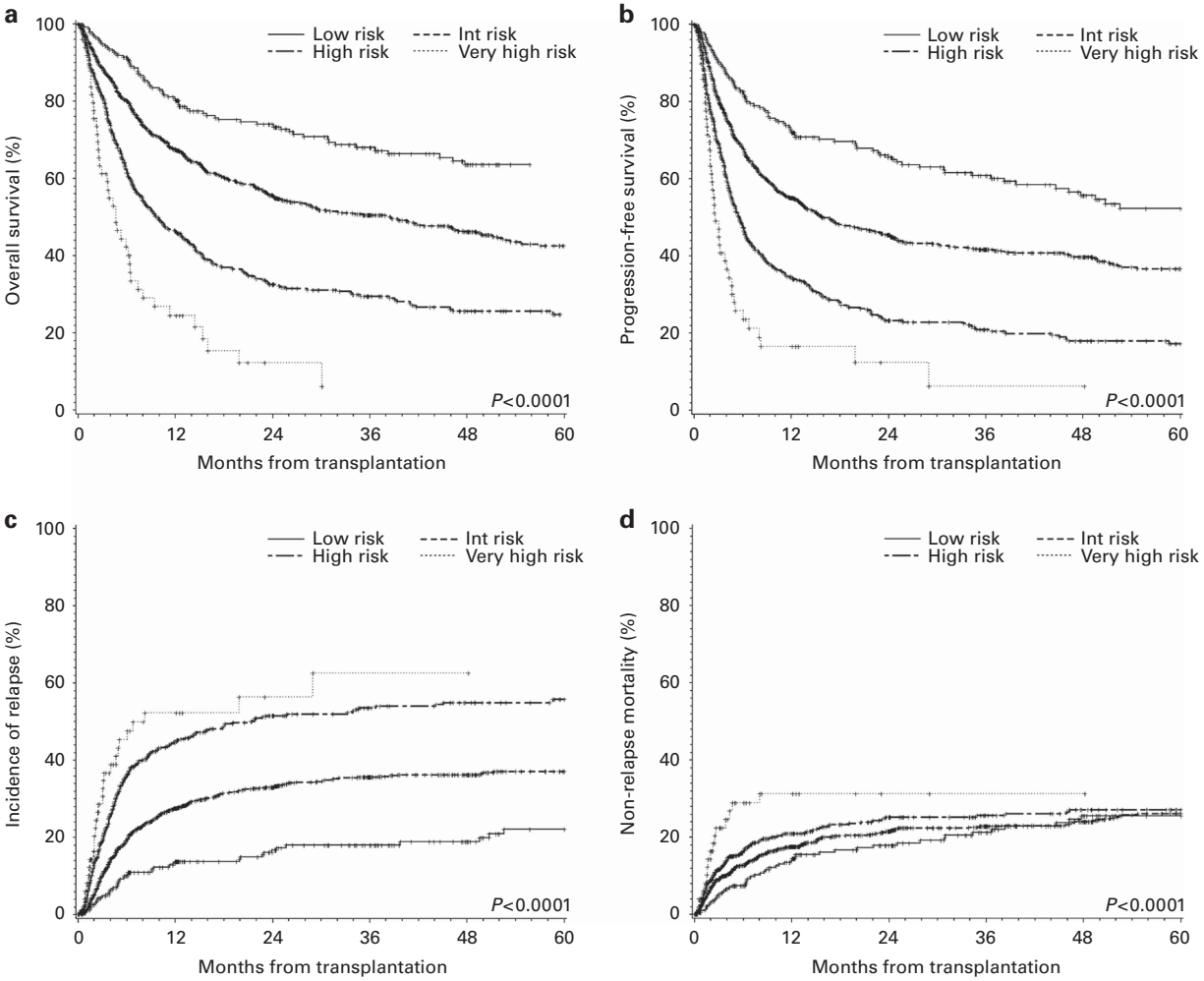

Figure 3. Risk stratification by disease-risk index categories for (**a**) overall survival, (**b**) PFS, (**c**) cumulative incidence of relapse and (**d**) cumulative incidence of non-relapse mortality. This research was originally published in *Blood*. Armand *et al.*[2] © American Society of Hematology.

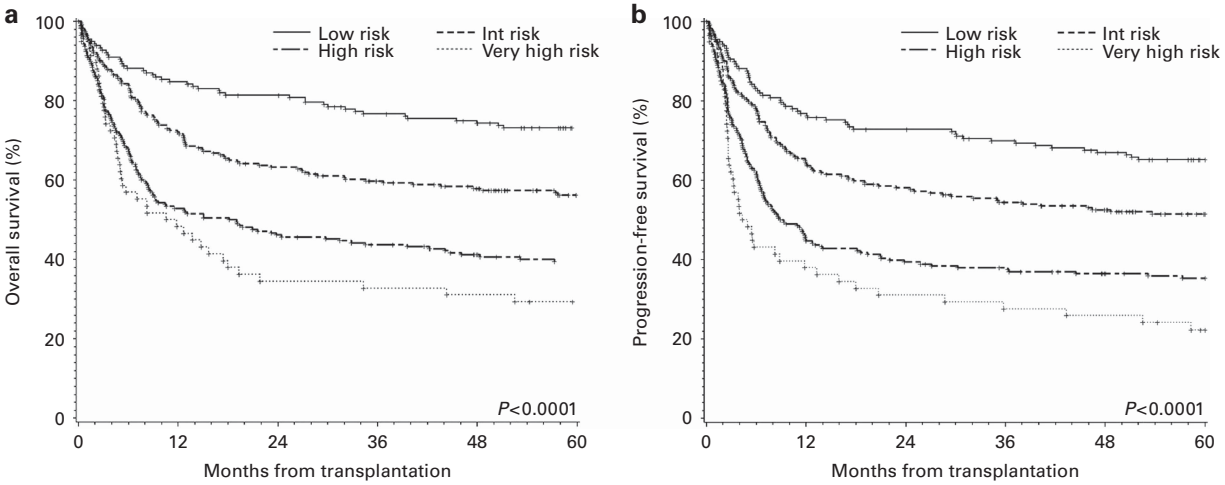

Figure 4. Validation of the disease-risk index in an independent cohort of 672 patients. (**a**) Overall survival; and (**b**) PFS. This research was originally published in *Blood*. Armand *et al.*[2] © American Society of Hematology.

The refined index could not demonstrate significant difference in OS between lymphoma patients, who received HCT in their first or second CR. However, their outcomes were better than those in any PR. This observation should be interpreted cautiously given the difference in conditioning intensity between the two groups. Also, more recent evidence suggests that there is no association between achieving CR as assessed by pretransplant ^{18}F-fluorodeoxy glucose–positron emission tomography scan and

Table 7. Validation of the DRI in single and multi-center studies

Study	*Number of patients*	*Types of donors*	*Conditioning intensities*	*outcomes*		*Comments*
				Predicted	*Not predicted*	
Armand *et al.*[61]	13 131	Related (42%) Unrelated (57%) Unknown (1%)	MA (53%) NMA/RIC (47%)	2-year OS	—	Diagnoses: malignant and non-malignant hematologic disorders. Building a new refined model
Beauverd *et al.*[86]	409	Related ($n=219$) Unrelated ($n=190$)	MA = 266 RIC = 143	4-year OS, PFS and relapse incidence	4-year TRM	Diagnoses: malignant and non-malignant hematologic disorders. 64% of grafts are T-cell depleted
Servais *et al.*[66]	442	Related ($n=138$) Unrelated ($n=164$)	MA ($n=138$) RIC ($n=304$)	5-year OS, PFS and relapse for very high-risk group	5-year OS, PFS and relapse for other groups	Diagnoses: malignant and non-malignant hematologic disorders. The inclusion of children and the higher inclusion of patients diagnosed with myeloma and MPN compared with the original study might have been responsible for the weaker association with outcomes. Accordingly, adapted DRI was developed by modifying original DRI could predict relapse and PFS
Lim *et al.*[62]	466	Related ($n=306$) Unrelated ($n=144$) UCB ($n=16$)	MA ($n=297$) NMA/ RIC ($n=169$)	4-year PFS, OS and CIR	NRM	Diagnoses: malignant and non-malignant hematologic disorders. Failed in smaller samples $\leqslant 50$ patients and shorter follow-up periods $\leqslant 40$ mo.

Abbreviations: CIR = cumulative incidences of relapse; DRI = disease-risk index; MA = myelobalative; mo = month; MPN = myeloproliferative; NMA = nonmyeloablative; NRM = non-relapse mortality; OS = overall survival; RIC = reduced-intensity conditioning; TRM = transplant-related mortality, UCB = umbilical cord blood.

post-allogeneic HTC survival for patients with lymphoma.[63] Prior autologous HCT for lymphoma had no significant influence on survival in multivariate models (HR = 1.1; $P = 0.2$).

The authors suggested using the DRI with its four risk categories in studies with a cohort size of >300 patients, while collapsing it into three categories (by merging high- and very high-risk groups into one group) in studies with a cohort size of <300 patients. A group of investigators from Europe modified the DRI to resolve its limited power of discrimination in their patient cohort. They moved the diagnoses of myeloproliferative neoplasms (MPN) and multiple myeloma from the intermediate-risk disease category and reassigned them to low- and high-risk groups, respectively, to develop an adapted DRI (aDRI). This modification was based on observations from previous studies, where patients with MPN tended to have relatively favorable outcomes,[10,64] although those with myeloma were noted to have relatively poor outcomes following allogeneic HCT.[65] Risk groups of the aDRI could successfully stratify hazards of relapse ($P < 0.05$) and PFS for high- and very high-risk groups, ($P < 0.05$) but not OS ($P > 0.09$). Compared with original DRI, aDRI had a higher discriminative capacity for relapse (c-statistics = 0.563 versus 0.631; $P = 0.005$, respectively) and, to a lesser extent, for PFS (c-statistics = 0.540 versus 0.572; $P = 0.04$, respectively).[66] Lack of a benefit in predicting OS brings the value of this adaption into question, particularly as OS was the outcome of interest in the original study of DRI.

COMBINED PATIENT- AND DISEASE-CENTERED RISK-ASSESSMENT MODELS

EBMT score

Development. EBMT risk score is one of the earliest models that was designed to provide assumptions about post-transplant risks of NRM, relapse and survival. Investigators from Europe analyzed the impact of a number of pretransplant variables on HCT outcomes among a cohort of 3142 patients diagnosed with CML, the most common diagnosis treated by HCT at that time.[67] In multivariate models, investigators identified five different variables to be statistically significantly associated with outcomes. Results were used to build a five-component scoring model with a total score ranging from 0 to 7 (Table 9).[3]

The new model was predictive of leukemia-free survival, OS and transplant-related mortality (TRM) at 5 years among patients with CML in the era before the discovery of tyrosine kinase inhibitors (TKIs). Rates of 5-year OS ranged between 72% and 22% for scores of 0 and 6, respectively.[67]

Validation. Multiple studies were conducted to validate the EBMT model. Results are summarized in Table 10.

Advantages. The EBMT model is a relatively simple one. Its components are well known and readily available to transplant physicians. This simplicity allows for ease of use and widespread applicability. Its development and validation were done in a number of studies that comprised large numbers of patients with heterogeneous characteristics, allowing for generalizability of its use. The model can be used equally well in patient cohorts with a single diagnosis, as well as multiple ones. In addition, components of the model capture different aspects of a patient's health, as well as some disease-specific risk factors suggesting its suitability for prediction of OS.

Limitations. Although the EBMT score is considered to be a generalized model comprising a set of variable patient-, disease- and transplant-related factors, it has a relatively modest discriminative capacity with *c*-statistic estimate of 0.63.[3] This could be due to a number of reasons:

Table 8. Differences in diseases risk assignments between original and refined DRI

Disease	*Original DRI risk category*	*Refined DRI risk category*
HL in CR	Intermediate	Low
MCL in CR	Intermediate	Low
Advanced stage AML with favorable CG	Intermediate	High
Advanced stage high-risk MDS with intermediate CG	Intermediate	High
ALL in 2nd CR	Intermediate	High
ALL in 3rd CR	Intermediate	High
CML in blast phase	Intermediate	Very high
Early stage low-risk MDS with adverse CG	High	Intermediate
Advanced stage ALL	High	Very high
Advanced stage aggressive NHL	High	Very high
Advanced stage high-risk MDS with adverse CG	Very high	High
Advanced stage low-risk MDS with adverse CG	Very high	High

Abbreviations: CG = cytogenetics; DRI = disease-risk index; HL = Hodgkin's lymphoma; MCL = mantle cell lymphoma; MDS = myelodysplastic syndromes; NHL = non-Hodgkin lymphoma.

First, cutoffs for some of its components are arbitrary and outdated. For example, age cutoffs were set for an era when only high-dose conditioning was offered to patients younger than 50 years old. Hence, there is no age categorization beyond 40 years in the model. The unaccountability of some important prognostic factors such as comorbidity and performance status might also be responsible for the modest prognostic power of the EBMT score. Further, disease stage categorization in the EBMT score is far less detailed than in the DRI classification. The EBMT model does not account for the impacts of cytogenetics or molecular markers. Although the EBMT model assigns a higher score for grafts from HLA-matched unrelated versus related donors, this impact is limited to allogeneic HCT following high-dose regimens and to an era when HLA matching was done using six antigens tested by low-resolution techniques. Recent studies have shown comparable outcomes between 10/10 HLA-unrelated and identical siblings among recipients of RIC regimens.[68]

The relative importance of some components is also questionable. For example, scores of 0 versus 1 are assigned to an interval between diagnosis and HCT of less versus >12 months, respectively. A long period between diagnosis and HCT could, on one hand, reflect disease aggressiveness requiring more chemotherapy to achieve remission before HCT or, on the other hand, could represent a disease with an indolent course not requiring early HCT. Nevertheless, this may not be essentially true for diseases such as acute leukemia in first CR, in which this factor will be always set as 0. This factor could be further subdivided into two separate periods with discordant impacts on survival. A longer time from diagnosis to achieving remission is usually associated with higher risk of relapse after HCT and hence lower OS. In contrast, a longer time from remission to transplant could be associated with lower relapse rates, lower risk of NRM and better OS.[3,69]

Modifications. In an effort to address some of the limitations of the model, a modified EBMT (mEBMT) score was developed. In the mEBMT score, interval between diagnosis and HCT was omitted, given its strong association with disease stage. Also, an extra point was given for patients >60 years, assuming their vulnerability to higher mortality risks. In multivariate analysis, HR per score unit for OS, NRM and relapse mortality were 1.5 ($P<0.001$), 1.36 ($P=0.042$) and 1.68 ($P<0.001$), respectively.[32] These modifications remain arbitrary and not based on a well-designed analysis to explore their impacts on outcomes. For example, age was recently shown to have a limited impact on outcomes when comorbidities are accounted for, and that impact was restricted to those of 40 years or less versus older patients.[46] Nevertheless, the mEBMT score performed better compared with the original score in a cohort of 306 recipients of RIC HCT for prediction of 4-year OS rates, $P=0.001$ and 0.06, respectively.[70]

Table 9. Components of EBMT risk score[87]

Risk factor	*Score*
Patient age (years)	
>20	0
20–40	1
>40	2
Disease stage[a]	
Early	0
Intermediate	1
Late	2
Time interval from diagnosis to transplant (months)[b]	
<12	0
>12	1
Donor type[c]	
HLA-identical sibling	0
Unrelated, other	1
Donor recipient sex combination	
All other	0
Female donor, male recipient	1

Reprinted by permission from Gratwohl.[3] [a]Early disease stage includes: acute leukemia (AL) transplanted in first CR, myelodysplastic syndromes (MDS) untreated or in first CR, CML in first chronic phase, and lymphoma and myeloma transplanted either untreated or in first CR. Intermediate disease stage includes: AL in second CR, CML at all other stages than first chronic phase or blast crisis, MDS in second CR or in PR, lymphoma and myeloma in second CR, in PR or in stable disease. Late disease stage includes: AL in all other disease stages, and lymphoma and myeloma in all disease stages other than defined as early or intermediate. No applicable stage for aplastic anemia (score 0). [b]Does not apply for patients transplanted in first CR (score 0). [c]Does not apply for autologous transplantation.

In a study of 502 leukemia patients who received haploidentical grafts, the donor type component was categorized according to the number of mismatched HLA loci, given the differences in incidence of NRM among different HLA mismatch categories. A score of 0, 1 or 2 was assigned to grafts with either single, double or triple mismatched loci, respectively, to develop a haplo-EBMT score. The EBMT score was significantly predictive of incidences of NRM ($P<0.001$), leukemia-free survival rates ($P<0.001$), incidences of relapse ($P=0.004$) and OS rates ($P<0.001$), respectively.[71]

Table 10. Validation of the EBMT risk score in single and multi-center retrospective studies

Study	*Number of patients*	*Types of donors*	*Conditioning intensities*	*Outcomes*		*Comments*
				Predicted	*Not predicted*	
Passweg *et al.*[88]	3211	Related (75%) Unrelated (25%)	MA	5-year OS	—	Diagnosis: CML. Analysis of data reported by 234 centers worldwide to the International Bone Marrow Transplantation Registry.
De Souza *et al.*[89]	1084	Related (95%) Unrelated (5%)	MA (86%) Others (14)	TRM, OS, DFS and RR for EBMT scores 5–6	—	Diagnosis: CML. Authors have shown that the EBMT model could help in selecting candidates who could potentially benefit from allogeneic HCT compared with TKIs.
Terwey *et al.*[32]	151	HLA matched ($n=134$) HLA-MM ($n=17$)	MA ($n=138$) RIC ($n=13$)	5-year NRM, OS and relapse mortality	—	Diagnosis: ALL. mEBMT score omitting time interval from diagnosis to transplant.
Gratwohl *et al.*[87]	56 505	Related (74%) Unrelated (24%)	MA (86%) RIC (14%)	5-year TRM and OS	—	Diagnoses: malignant and non-malignant hematologic disorders. The analysis aimed at exploring the prognostic value of the EBMT model in diseases other than CML utilizing large registry data set of patients with different hematological disorders, who received their first allogeneic HCT at different centers in Europe. Results supported expanding the use of EBMT risk score to hematological disorders other than CML.
Lodewyck *et al.*[90]	327	T-cell depleted unrelated grafts	MA ($n=256$) Others (n = 71)	5-year NRM and OS	—	Diagnosis: poor risk AML and MDS. Incorporation of high resolution HLA typing with EBMT scores resulted in better prognostication.
Barba *et al.*[70]	306	Related (230) Unrelated (76)	RIC	4-year NRM and OS	—	Diagnoses: malignant hematologic disorders. mEBMT score provided better prediction compared with classical EBMT score.
Rezvani *et al.*[91]	124	HLA matched ($n=107$) HLA-MM ($n=17$)	MA ($n=72$) RIC ($n=52$)	5-year NRM and OS	—	Diagnoses: recipients of a second transplantation for malignant and non-malignant hematologic disorders. A combined model of EBMT scores and time from first to second transplantation independently predicted outcomes.
Pitombeira *et al.*[92]	278	Related ($n=238$) Unrelated (40)	MA ($n=241$) RIC ($n=37$)	5-year NRM and OS	RR	Diagnoses: malignant and non-malignant hematologic disorders.
Wallet *et al.*[93]	136	UCB	MA ($n=46$) RIC ($n=90$)	3-year TRM, OS and RR	—	Diagnoses: malignant and non-malignant hematologic disorders.
Wang *et al.*[71]	502	Haploidentical grafts	MA	NRM, LFS and OS	—	Diagnoses: acute and chronic leukemia. Adapted a modified Haplo-EBMT score based on number of MM HLA loci.

Abbreviations: DFS = disease-free survival; EBMT = European Society for Blood and Marrow Transplantation; LFS = leukemia-free survival; MA = myelobalative; MDS = myelodysplastic syndromes; mEBMT score = modified EBMT score; MM = mismatched; NRM = non-relapse mortality; OS = overall survival; RIC = reduced-intensity conditioning; RR = relapse rate; TKI = tyrosine kinase inhibitor; TRM = transplant-related mortality; UCB = umbilical cord blood.

Table 11. Components and categories of pretransplantation assessment of mortality score (PAM score)

Age (years)	*Score*
< 20	1
20–30	1
30–40	1
40–50	1
50–60	3
> 60	5
Donor type	
Matched related	1
Unrelated	3
Mismatched related	4
Disease risk	
Low	1
Intermediate	8
High	12
Conditioning regimen	
Nonmyeloablative	1
Non-TBI	4
TBI with ⩽12 Gy	8
TBI with >12 Gy	9
Serum creatinine level	
⩽1.2 mg/dL	1
>1.2 mg/dL	8
Serum ALT level	
⩽49 U/L	1
>49 U/L	2
FEV1	
>80%	1
70-80%	3
<70%	6
Corrected DLco	
>80%	1
70-80%	1
<70%	4

Category	*Original score*	*Modified score*
1	9–16	8–19
2	17–23	20–25
3	24–30	26–30
4	31–44	31–50

Abbreviations: ALT = alanine aminotransferase; DLco = diffusion capacity of the lung for carbon monoxide; FEV1 = forced expiratory volume in 1 s. Low-risk diseases included: CML in chronic phase, refractory anemia, aplastic anemia and the Blackfan–Diamond syndrome. Intermediate-risk diseases included: CML in accelerated phase or chronic phase after blastic phase, acute leukemia or lymphoma in remission, refractory anemia with excess blasts, chronic lymphocytic leukemia and paroxysmal nocturnal hemoglobinuria. High-risk diseases included: CML in blastic phase, juvenile CML, acute leukemia or lymphoma in relapse, refractory anemia with excess blasts in transformation, myeloma, solid tumors and non-hematologic diseases.

PAM score

Development. The PAM score was developed as a model to predict all-cause mortality during the immediate 2-year period, following allogeneic HCT in 2802 patients treated between 1990 and 2002 at FHCRC. Patients were randomly divided into two equal cohorts for the model development and validation. The validation cohort ($n = 1401$) was further subdivided into an early subgroup ($n = 853$), for patients given HCT before 1 January 1998, and a late subgroup ($n = 548$), for patients given HCT thereafter, to account for the introduction of nonmyeloablative transplant protocols.[4] In multivariate analysis, eight risk factors were found to significantly impact HCT outcome. Accordingly, the authors designed a 50-point model from those factors (Table 11). The model stratified patients into four categories with scores ranging from 8 to 50 points with statistically significantly different 2-year probabilities of mortality for risk categories of 1–4 ranging from 16 to 81% in the early validation cohort and from 8 to 82% in the late validation cohort, respectively ($P < 0.001$). Authors then performed internal validation of the PAM score utilizing three subgroups from the same institution. These subgroups comprised the three most frequently observed diagnoses in the entire cohort: CML ($n = 1017$) AML ($n = 667$) and MDS ($n = 407$). *C*-statistic estimates ranged between 0.69 and 0.76 for all validation cohorts.[4]

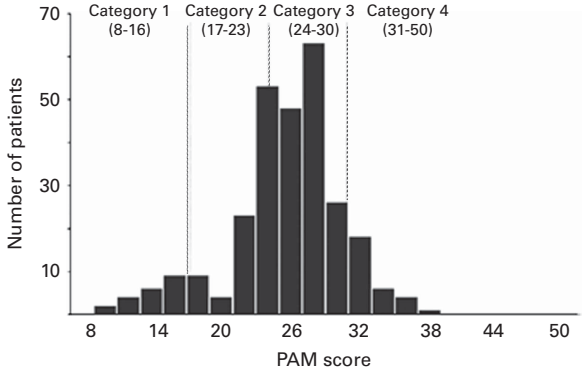

Figure 5. Histogram of distribution of PAM scores in 276 allogeneic HCT recipients. Majority of patients clustered in categories 2 and 3 with very few patients in categories 1 and 2. Reprinted by permission from Mori *et al.*[72]

Validation. In a group of 276 non-Caucasian patients, investigators attempted to validate the PAM model. There was an uneven distribution of patients in the different risk categories, with 16% and 66% of patients being assigned to categories 2 and 3, respectively (Figure 5). Thus, authors modified score categories to allow a more even distribution of patients by slightly changing cutoff values between the different categories (Table 11). In the modified model, categories 2 and 3 included 29% and 47% of patients, respectively. Overall, c-statistics were slightly higher for the modified compared with the original model (0.74 versus 0.70). No *P*-value estimate for the difference between the two *c*-statistic estimates was provided.[72]

In another study, investigators failed to validate the prognostic capacity of the PAM score in a cohort of 194 RIC HCT recipients. The model was not predictive of rates of 2-year OS ($P = 0.11$) nor incidences of NRM ($P > 0.4$).[20] Similarly, the limited predictive power of the PAM score was demonstrated in a small study, where the model failed to predict hazards of 2-year OS ($P = 0.2$) or 100- day TRM ($P = 0.08$) in a cohort of 63 HCT recipients who were >60 years of age.[35]

Advantages. The PAM score incorporates some significant comorbidities, as well as some disease - and HCT-specific features to create a single model. This mix of variables allows for a global assessment of overall mortality.

Limitations. The external validity of the PAM score remains controversial with contradicting reports from different institutions.[20,31] Another caveat is under-representation of older patients, with only 4% of patients being older than 60 years. In addition, disease categories were not represented equally in the cohort, with almost 75% of patients carrying only three diagnoses,

CML, AML and MDS. This finding could limit reproducibility of results when encountering a more heterogeneous population of HCT recipients. Although PAM score included conditioning intensity as a variable, growing evidence suggests its minor impact on HCT outcomes.[2,61]

Recently, the PAM score has been shown to be a better predictor of 2-year post-transplant mortality among recipients of high-dose compared with RIC allogeneic HCT. Each point increase in the PAM score correlated with 10% versus 6% increase in risks of 2-year mortality following high-dose versus RIC allogeneic HCT, respectively ($P = 0.002$). *C*-statistics estimates were higher among recipients of high-dose compared with RIC allogeneic HCT, 0.64 and 0.57, respectively.[73] This significantly precludes the model usefulness for predicting outcomes for the rapidly growing population of RIC allogeneic HCT recipients.

Modifications. To allow more even distribution of patients, the cutoff values for PAM risk categories were modified (Table 11).[72] The original developers of the model showed some variables to lose their prognostic association with 2-year mortality rate over time in a cohort of 1549 recipients of allogeneic HCT between 2003 and 2009. As a result,

- Diffusion capacity of the lungs for carbon monoxide, serum alanine aminotransferase and serum creatinine levels were omitted.
- Patient and donor CMV serostatus combinations were added.
- Disease risk was reorganized as per the DRI risk classification system.[2]
- Degree of HLA matching was used to re-categorize the unrelated donor group.

These modifications resulted in a revised PAM score.[73] The revised PAM model had closely similar bias-corrected Akaike information criteria (5011.5 versus 5042.3) and bias-corrected *c*-statistic values (0.65 versus 0.64) compared with the original model. Investigators found that the revised PAM model provides better prediction for recipients of high-dose conditioning regimen.[73]

SUMMARY AND FUTURE DIRECTIONS

The optimal decision-making process before allogeneic HCT should carefully weigh the risks of disease relapse, as well as those of NRM. The HCT-CI provides specific information about patient tolerability to the transplant process. The index stratifies well the probabilities of NRM. This was further enhanced by creating the composite age/comorbidity[46] and the augmented HCT-CI incorporating some laboratory biomarkers.[47] On the other hand, the newly developed DRI was shown to be a refined tool for assessment of relapse probabilities. In the clinic, the simultaneous use of both indices would probably provide the most accurate and precise prediction of survival rates after transplant. The main concept would be the greater the risk of relapse per the DRI criteria and the greater the need for allogeneic HCT and for higher-intensity conditioning regimen, the higher the maximum HCT-CI score that would make a patient eligible for HCT and vice versa.

CGA is another promising tool to predict outcomes in elderly HCT recipients.[43] However, it needs to be validated in large multi-center studies to properly identify its most useful components in the setting of HCT. The Comorbidity and Regimen-related Toxicity Committee of the Blood and Marrow Transplantation-Clinical Trial Network proposed a novel study to create a composite health model incorporating the HCT-CI, performance status, some geriatric assessment tools and molecular biomarkers[15] to further enhance prediction of NRM.[74] On the other hand, molecular markers of the primary malignancy could be incorporated in the future to further improve the predictive power of the DRI.

Global risk models such as PAM or EBMT target OS as the primary assessed outcome. These models could provide a second layer of evaluation to support conclusions made by the combined use of specific models for NRM and relapse. The newly modified PAM model is made specifically for recipients of high-dose conditioning regimens. EBMT could be combined with HCT-CI to enhance prediction of survival.[42]

The future of risk stratification will increasingly rely on objective and more advanced data. Whole-genome sequencing, gene expression profiling[75] and expression of micro-RNAs[76,77] are likely to be used in prediction of relapse. Similarly, information on single-nucleotide polymorphisms[78] non-HLA genetic variants[79] and biomarkers for acute GvHD[80,81] could be used to stratify risks of NRM. These potential future changes promise an individualized approach in decision-making and patient care before and after HCT.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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