Comorbidity-Age Index: A Clinical Measure of Biologic Age Before Allogeneic Hematopoietic Cell Transplantation

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ABSTRACT

Purpose

Age has long been used as a major factor for assessing suitability for allogeneic hematopoietic cell transplantation (HCT). The HCT-comorbidity index (HCT-CI) was developed as a measure of health status to predict mortality risk after HCT. Whether age, comorbidities, or both should guide decision making for HCT is unknown.

Patients and Methods

Data from 3,033 consecutive recipients of HLA-matched grafts from five institutions contributed to this analysis. Patients were randomly divided into a training set to develop weights for age intervals and a validation set to assess the performance of prognostic models.

Results

In the training set, patients age 20 to 39 years, 40 to 49 years, 50 to 59 years, and ≥ 60 years had hazard ratios for nonrelapse mortality (NRM) of 1.21 ($P = .29$), 1.48 ($P = .04$), 1.75 ($P = .004$), and 1.84 ($P = .005$), respectively, compared with those age younger than 20 years. Consequently, age ≥ 40 years was assigned a weight of 1 to be added to the HCT-CI to constitute a composite comorbidity/age index. In the validation set, the composite comorbidity/age score had statistically significantly higher c-statistic estimates for prediction of NRM (0.664 v 0.556; $P < .001$) and survival (0.682 v 0.560; $P < .001$) compared with age, respectively. Patients with comorbidity/age scores of 0 to 2 had comparable mortality risks regardless of conditioning regimens. Patients with scores of 3 to 4 and ≥ 5 had statistically significant higher mortality risks after high-dose versus nonmyeloablative regimens.

Conclusion

Age is a poor prognostic factor. The proposed composite measure allows integration of both comorbidities and age into clinical decision making and comparative-effectiveness research of HCT.

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INTRODUCTION

Decision-making information that takes into account the complexity of different risk factors is important in guiding the choice of the appropriate regimen for allogeneic hematopoietic cell transplantation (HCT). During the past 50 years, major advances have been made in our understanding of the impacts of disease-specific risk factors (eg, chromosomal aberrations and gene expression profiles^{1,2}) and transplantation-specific risk factors (eg, the choice of donor grafts³⁻⁵ or stem-cell source⁶). On the other hand, until recently, age alone was the most widely used measure of a patient's ability to tolerate a given conditioning regimen for allogeneic HCT. Therefore, transplant protocols have typically been divided into those suitable for older patients

versus those suitable for younger patients with an arbitrary cutoff range of 55 to 60 years between the two groups.

Yet the prognostic role of age in the HCT setting has never been consistent. Earlier studies of high-dose regimens identified an adverse impact of patient age on nonrelapse mortality (NRM) after HCT,⁷⁻¹⁰ but more recent studies of lower-intensity regimens have shown conflicting results regarding the association between age and outcomes.¹¹⁻¹⁵ None of the previous studies have taken into account the confounding effect of organ comorbidities on outcomes. As a result, providing transplant recommendations on the basis of patient health status versus age has lacked an evidence base.

Compromised organ functions (comorbidities) impact the therapeutic planning and outcome

of any treatment.¹⁶ The advent of the HCT-comorbidity index (HCT-CI) as a measure of health status at the time of HCT with emphasis on individual organ dysfunction has facilitated the incorporation of comorbidities into the pre-HCT assessment of patients.¹⁷ During the past few years, comorbidity evaluation has advanced HCT outcome research by providing important risk assessment information before HCT.¹⁸⁻²² Although these results have improved the evaluation of health status before HCT, many contemporary HCT protocols are still age-dependent, with criteria limited to patients either younger or older than an arbitrary age cutoff.

Therefore, an important question remained as to how to integrate both age and comorbidities in selecting the appropriate regimen for allogeneic HCT. We conducted a large multi-institutional retrospective study to assess whether age has any remaining role in outcome prediction in models containing the HCT-CI and whether a single measure incorporating both age and comorbidities could be developed and used to compare the effectiveness of different intensities of conditioning regimens.

PATIENTS AND METHODS

Patients

In 2007, a multi-institutional retrospective study was approved by the internal review boards of all participating institutions. Data stored in institution computerized databases were retrieved by data managers from all five institutions for patients meeting the following criteria: (1) received diagnoses of hematologic malignant or nonmalignant diseases, (2) treated with allogeneic HCT between 2000 and 2006, (3) received any type of conditioning regimen, (4) received grafts from HLA-matched related or unrelated donors, and (5) received marrow or granulocyte colony-stimulating factor–mobilized peripheral blood mononuclear cells as the graft source. Details about data collection and study definitions are provided in the Data Supplement.

Statistical Methods

To develop and assign weights to age intervals, patients were randomly divided into two cohorts; 1,853 patients were assigned to a training set, and 1,180 patients were assigned to a validation set. Integer weights for age intervals were derived from Cox proportional hazards modeling applied to the training set, with NRM as the outcome. Hazard ratios (HRs) for NRM were calculated for each age interval, controlling for the presence of all covariables described in Table 1 including HCT-CI scores and conditioning intensity. Multivariable *P* values for each variable were based on adjustment for all other variables in the model. All *P* values were derived from likelihood ratio statistics and were two-sided. The adjusted HRs were converted to integer weights according to our previously published criteria.¹⁷ The composite comorbidity/age score was the sum of the score assigned to the HCT-CI plus that assigned to age for each individual patient.

In the validation set, we compared the capabilities of age versus the HCT-CI versus the composite index to discriminate risks for NRM and survival. Comparisons were done by computing the c-statistic²³ with the same interpretation of results as previously described.¹⁷ The c-statistic was computed on the basis of time to event, using the entire follow-up period. SEs for the c-statistic were estimated by applying a bootstrap procedure to the validation data set, using 50 bootstrap samples. Similarly, the SE for the difference in c-statistic between the three indices were estimated from the bootstrap samples and used to calculate a z-score and *P* value for the difference.

Outcomes according to the three conditioning modalities, stratified by the new composite comorbidity/age score, were compared using the entire patient sample to ensure adequate power to detect the differences in survival. Because no direct comparisons of outcomes on the basis of age or HCT-CI/age scores were made in these subset analyses, inclusion of patients from the training set that was used to develop the age scores was not thought to bias the comparison of outcomes on the basis of conditioning regimen intensity. Ad-

justed survival curves were estimated on the basis of methods described by Makuch²⁴ (Data Supplement).²⁵

RESULTS

Patient Characteristics

Among 3,335 patients who met the study criteria, 302 were excluded from the analyses as a result of lack of comorbidity data (*n* = 267) or lack of data on patient cytomegalovirus serology results (*n* = 35), yielding a final sample size of 3,033. Patient characteristics are described in Table 1.

Role of Age in Predicting NRM After Allogeneic HCT

Increasing age was significantly associated with NRM in a model adjusted for all risk factors, including the HCT-CI (Table 2). In the training set, patients in the age groups of 20 to 39, 40 to 49, 50 to 59, and ≥ 60 years had HRs for NRM of 1.21 (*P* = .29), 1.48 (*P* = .04), 1.75 (*P* = .004), and 1.84 (*P* = .005), respectively, compared with those younger than age 20 years.

Development of the Composite Comorbidity/Age Index

In the training set, the HRs for NRM were not statistically significantly different when comparing patients of ≥ 60 years with those of 40 to 49 (*P* = .17) and 50 to 59 (*P* = .71) years. Visual illustration of the relationship between age, as a continuous variable, in years and the adjusted HR for NRM confirmed lack of an abrupt increase in risks of mortality beyond age 40 years (Fig 1). Given that patients in the age groups 40 to 50, 50 to 60, and older than 60 years had HRs for NRM ranging between 1.48 and 1.84 compared with patients younger than age 20 years, age ≥ 40 years was assigned a score of 1 to be added to the HCT-CI scores, following the same approach used for development of the HCT-CI.¹⁷

Validation of the Composite Comorbidity/Age Index

In the validation set, the composite index had statistically significantly higher c-statistic estimates for NRM (0.677) and survival (0.653) compared with age alone (0.549 and 0.547, respectively; *P* < .001 for both). These estimates for the composite index were also better compared with the HCT-CI (0.675 and 0.649, respectively), but the differences did not reach statistical significance (*P* = .56 and *P* = .28, respectively). In Cox regression models (Data Supplement Table S2), the composite comorbidity/age scores provided overall better stratifications of risks for NRM and survival compared with age and the HCT-CI (Fig 2).

Age of ≥ 40 years was consistently associated with both higher cumulative incidences and higher adjusted HRs for NRM among the three conditioning intensities (Table 3). Finally, the improvements in c-statistic estimates for NRM with the composite comorbidity/age scores compared with age were consistent among recipients of high-dose (0.681 v 0.568), reduced-intensity (0.641 v 0.548), or nonmyeloablative regimens (0.653 v 0.531).

Comparative Effectiveness of Conditioning Intensities Using the Composite Comorbidity/Age Index

Patients with low (0 or 1-2) composite comorbidity/age scores had comparable survival rates (Data Supplement Figure S2) and no

Comorbidity and Age in Allogeneic Transplantation

Table 1. Patient, Transplantation, and Disease Characteristics

Characteristic	Conditioning Regimens Classified According to Intensity							
	All Patients (N = 3,033)		High Dose (n = 1,889)		Reduced Intensity (n = 465)		Nonmyeloablative (n = 679)	
	No.	%	No.	%	No.	%	No.	%
HCT-CI score								
0	956	31.5	702	37.2	99	21.3	155	22.8
1	450	14.8	311	16.5	58	12.5	81	11.9
2	495	16.3	292	15.5	72	15.5	131	19.3
3	543	17.9	297	15.7	108	23.2	138	20.3
4	267	8.8	139	7.4	57	12.3	71	10.5
5	163	5.4	80	4.2	34	7.3	49	7.2
≥ 6	159	5.2	68	3.6	37	8.0	54	8.0
Age, years								
≤ 19	406	13.4	333	17.6	32	6.9	41	6.0
20-39	767	25.3	607	32.1	83	17.9	77	11.3
40-49	705	23.2	486	25.7	98	21.1	121	17.8
50-59	768	25.3	395	20.9	145	31.2	228	33.6
≥ 60	387	12.8	68	3.6	107	23.0	212	31.2
KPS, %								
95-100	1,156	38.1	804	42.6	148	31.8	204	30.0
85-90	1,117	36.8	680	36.0	188	40.4	249	36.7
95-80	529	17.4	301	15.9	85	18.3	143	21.1
≤ 70	231	7.6	104	5.5	44	9.5	83	12.2
No. of prior regimens								
0	469	15.5	291	15.4	96	20.7	82	12.1
1-2	1,274	42.0	891	47.2	158	34.0	225	33.1
3-4	917	30.2	539	28.5	149	32.0	229	33.7
≥ 5	373	12.3	168	8.9	62	13.3	143	21.1
Donor								
Related	1,677	55.3	1,069	56.6	240	51.6	368	54.2
Unrelated	1,356	44.7	820	43.4	225	48.4	311	45.8
Stem-cell source								
Marrow	660	21.8	548	29.0	69	14.8	43	6.3
PBMC	2,373	78.2	1,341	71.0	396	85.2	636	93.7
ATG in conditioning								
Yes	243	8.0	103	5.5	116	25.0	24	3.5
No	2,790	92.0	1,786	94.6	349	75.1	655	96.5
Diagnosis*								
Myeloid	1,816	59.9	1,268	67.1	271	58.3	277	40.8
Lymphoid/plasma cell	1,028	33.9	563	29.8	142	30.5	323	47.6
Other malignant	63	2.1	21	1.1	13	2.8	29	4.3
Nonmalignant	126	4.2	37	2.0	39	8.4	50	7.4
Risk of relapse†								
High	1,826	60.2	1,049	55.5	307	66.0	470	69.2
Low	1,207	39.8	840	44.5	158	34.0	209	30.8
CMV serostatus								
Positive	1,894	62.5	1,185	62.7	293	63.0	416	61.3
Negative	1,139	37.6	704	37.3	172	37.0	263	38.7

Abbreviations: ATG, antithymocyte globulin; CMV, cytomegalovirus; HCT-CI, hematopoietic cell transplantation–comorbidity index; KPS, Karnofsky performance status; PBMC, peripheral blood mononuclear cells.

*Myeloid malignancies included acute myeloid leukemia, biphenotypic leukemia, chronic myeloid leukemia, and myelodysplastic syndromes; lymphoid/plasma cell malignancies included acute lymphocytic leukemia, chronic lymphocytic leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, and plasma cell leukemia; and nonmalignant disease included aplastic anemia, sickle-cell anemia, autoimmune disease, and other hematologic nonmalignant diseases.

†Low disease risk for relapse included acute leukemia in first complete remission; chronic myeloid leukemia in first chronic phase; myelodysplastic syndromes with refractory anemia or refractory anemia with ringed sideroblasts; chronic lymphocytic leukemia, lymphoma, or multiple myeloma in complete remission; and nonmalignant diseases. High disease risk for relapse included all other disease statuses.

statistically significant differences in HRs for survival after nonmyeloablative, reduced-intensity, or high-dose regimens (Table 4). Adjusted cumulative incidences for NRM at 2 years were 5%, 12%, and 10%, respectively, among patients with a score of 0 and 9%, 18%, and 20%,

respectively, among those with scores of 1 or 2 (Data Supplement Figure S1).

Patients with composite comorbidity/age scores of 3 or 4 had adjusted 2-year rates of survival of 59%, 50%, and 45%, respectively.

Table 2. Cox Regression Models for Risks of Nonrelapse Mortality in the Training Set (n = 1,853)

Characteristic	Nonrelapse Mortality*		
	HR	95% CI	P
Age, years			
≤ 19 (n = 245)	1.0		
20-39 (n = 475)	1.21	0.8 to 1.7	.29
40-49 (n = 429)	1.50	1.0 to 2.2	.03
50-59 (n = 457)	1.78	1.2 to 2.6	.003
≥ 60 (n = 247)	1.85	1.2 to 2.8	.004
HCT-CI score			
0 (n = 567)	1.0		
1-2 (n = 607)	2.15	1.6 to 2.8	< .001
≥ 3 (n = 679)	3.66	2.8 to 4.7	< .001
Donor			
Related (n = 1,024)	1.0		
Unrelated (n = 829)	1.42	1.2 to 1.7	.001
Regimen intensity			
High dose (n = 1,139)	1.0		
Reduced intensity (n = 284)	0.70	0.5 to 0.9	.01
Nonmyeloablative (n = 430)	0.61	0.5 to 0.8	.001
ATG in conditioning			
No (n = 1,707)	1.0		
Yes (n = 146)	0.90	0.6 to 1.3	.61
Disease category			
Myeloid (n = 1,108)	1.0		
Lymphoid/plasma cell (n = 639)	1.24	1.0 to 1.5	.04
Other malignant (n = 35)	0.72	0.3 to 1.6	.43
Aplastic anemia (n = 37)	1.38	0.5 to 3.6	.51
Other nonmalignant (n = 34)	4.65	2.4 to 9.0	< .001
Risk of relapse			
Low (n = 700)	1.0		
High (n = 1,153)	1.66	1.3 to 2.0	< .001
Stem-cell source			
Marrow (n = 373)	1.0		
PBSC (n = 1,480)	1.34	1.0 to 1.7	.03
CMV serology status			
Negative (n = 675)	1.0		
Positive (n = 1,178)	1.53	1.3 to 1.9	< .001
No. of prior regimens			
0-3 (n = 1,403)	1.0		
≥ 4 (n = 450)	1.14	0.9 to 1.4	.22
KPS, %			
> 80 (n = 1,388)	1.0		
≤ 80 (n = 465)	1.41	1.2 to 1.7	< .001

Abbreviations: ATG, antithymocyte globulin; CMV, cytomegalovirus; HCT-CI, hematopoietic cell transplantation-comorbidity index; HR, hazard ratio; KPS, Karnofsky performance status; PBMC, peripheral blood mononuclear cells.

*The model was also adjusted for institution via stratification.

Fig 1. Illustration of the relationship between age in years and the hazard ratio for nonrelapse mortality (NRM). Patients in the training group were sorted by age and divided into groups of 100 patients each. The dots represent the estimated hazard ratios for the association between each age group and NRM relative to a reference group (median age, 45 years; range, 42-49 years) using Cox regression models. A smooth curve fitted to the dots was generated to represent the relationship of age in years with NRM both before (black) and after (blue) adjustment for all other risk factors in the Cox regression model.

ablative, reduced-intensity, or high-dose regimens. NRM-adjusted incidences were 35%, 41%, and 49%, respectively.

Case presentations for the applicability of the composite comorbidity/age scores in decision making are provided in the Data Supplement.

DISCUSSION

The overarching goal of this study was to enhance our ability to make accurate predictions about the tolerability of allogeneic HCT so that this information can be factored into treatment decisions. For decades, chronologic age alone has been the primary determinant of patient eligibility for HCT as well as for a given conditioning intensity. Here, we have provided a careful quantification of the magnitude of the prognostic impact of age for HCT outcomes. Age of ≥ 40 years has a prognostic impact on NRM, but that impact is modest, given that it contributes the equivalent of a single comorbidity with a weight of 1 within the HCT-CI. Indeed, the c-statistic estimate for NRM was highly statistically significantly ($P < .001$) better for the combined comorbidity/age score (0.664) compared with that for age alone (0.556). The composite comorbidity/age index could be used by physicians and patients to accurately account for the impacts of age and comorbidities when making treatment decisions or estimating outcomes after allogeneic HCT with a variety of conditioning regimens.

With the proven value of the HCT-CI, it became important to delineate the relative prognostic role of age in HCT decision making. The relative roles of age versus the composite comorbidity/age scores can be further appreciated in the case summary presentations (Data Supplement Table S3). Patients older than age 60 years tolerated high-dose conditioning well if they were otherwise medically healthy, whereas those younger than age 60 or even 40 years succumbed more quickly to NRM if they had significant comorbidities. This finding should steer us away from the current practice in which patients are

Recipients of nonmyeloablative regimens (HR, 0.72; $P = .004$), but not those of reduced-intensity regimens (HR, 0.99; $P = .95$), had statistically significant lower risks for mortality compared with those of high-dose regimens. NRM incidences at 2 years were 17%, 36%, and 37%, respectively, after nonmyeloablative, reduced-intensity, or high-dose regimens. Likewise, patients with scores of ≥ 5 had statistically significant lower risks for mortality after nonmyeloablative (HR, 0.73; $P = .02$) but not reduced-intensity (HR, 0.86; $P = .29$) compared with high-dose regimens. Adjusted rates of 2-year survival among this risk category were 37%, 35%, and 29%, respectively, after nonmyelo-

Fig 2. Comparisons of outcome stratifications by the hematopoietic cell transplantation-comorbidity index (HCT-CI) and the composite comorbidity/age index (HCT-CI/age). (A, B) Cumulative incidences of nonrelapse mortality and (C, D) Kaplan-Meier estimates of overall survival among patients of the validation set ($n = 1,180$) as stratified by (A, C) the HCT-CI and (B, D) the composite comorbidity/age index.

assigned to conditioning regimens frequently according to age younger than 55 to 60 or older than 55 to 60 years.

Our study included patients from five US transplant centers given a wide variety of conditioning regimens, which would increase the likelihood of the generalizability of results. It remains to be seen how the composite comorbidity/age scores would perform in shaping the decision-making process at other institutions. In addition, our models were derived from retrospective data. Although prospective validation is often required; in this case, it might be hampered by ethical considerations resulting from, for example, the high risk of NRM associated with patients with high composite scores when given conventional high-dose regimens. However, some novel high-dose regimens have been associated with an overall relatively lower NRM²⁶; therefore, prospective assessment of tolerance of patients with high-risk comorbidities to these types of high-dose regimens could be of interest. Another limitation was the inclusion of patients ($n = 510$) who previously contributed to the development of the HCT-CI. However, a sensitivity analysis (Data Supplement) excluding this small sample of patients (16.8%) yielded results similar to those found among the whole study population, which suggests that including these patients did not bias the analyses. Data were analyzed from patients treated with HCT through the year 2006 to allow for enough

duration to capture the full impact of age and comorbidities on mortality.²⁷ Of note, recent studies have shown that the HCT-CI has stood the test of time by predicting outcomes among more recently treated patients.^{22,28} Our intent is for the composite index to be used by transplant as well as oncology physicians to continuously assess the choices for allogeneic HCT for their patients. However, use of the composite index might be undermined by the ease and availability of age. Understanding that the main burden on physicians is to calculate the HCT-CI score, it is now facilitated in a validated web-based application (www.hctci.org).²⁹ These features should encourage the routine use of the composite comorbidity/age scores instead of age in risk assessment before HCT.

Within the previous constraints, our findings convey several important clinical ramifications. First, the composite comorbidity/age scores could be used in designing randomized clinical trials to tease out the most appropriate conditioning regimen for a group of patients with a particular risk score. Second, outside randomized trials, the composite index could be used in the clinic to identify patients who might or might not benefit from allogeneic HCT as well as those who might benefit the most from high-dose versus lower-intensity regimens. This is particularly the case given that we have shown here consistent stratification of mortality risks by the composite index

Table 3. Cumulative Incidence and HR for Nonrelapse Mortality Stratified by Regimen Intensity and Age

Age Group by Regimen Intensity (years)	Cumulative 2-Year Incidence (%)	Univariable			Multivariable*		
		HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Myeloablative							
0-39	21	1.0			1.0		
≥ 40	32	1.58	1.3 to 1.9	< .001	1.35	1.1 to 1.6	.004
Reduced intensity							
0-39	24	1.0			1.0		
≥ 40	34	2.02	1.3 to 3.0	< .001	1.52	1.0 to 2.4	.07
Nonmyeloablative							
0-39	16	1.0			1.0		
≥ 40	23	1.68	1.0 to 2.8	.04	2.01	1.1 to 3.6	.02

Abbreviations: ATG, antithymocyte globulin; CMV, cytomegalovirus; HCT-CI, hematopoietic cell transplantation–comorbidity index; HR, hazard ratio; KPS, Karnofsky performance status.

*Cox regression models were adjusted for diagnosis category, disease risk, HCT-CI risk group, donor type, stem-cell source, KPS percentage, No. of prior regimens, use of ATG, and CMV serology status.

among patients with different diagnosis categories. Third, the model could be used to adjust comparisons of outcomes from different trials or different institutions.

Finally, we¹¹ and others^{12,13} have shown acceptable results for allogeneic HCT among patients older than age 60 or 65 years. Yet, only 12% and 6% of recipients of allogeneic HCT were age ≥ 60 or ≥ 65 years, respectively, and these proportions have not changed substantially for years³⁰⁻³²; this suggests that few clinicians are aware of the best way to choose candidates for this approach. Many patients remain poorly informed, fearful, and sometimes desperate with their aggressive malignancies in their sixties and seventies with no readily available tools to guide choice of therapy. This is unfortunate, given that the median age for the majority of hematologic malignancies is older than age 60 years and given that older patients are expected to constitute 20% of the total population by 2030.³³⁻³⁵ Implementation of the

composite comorbidity/age score in decision making about referral of older patients to allogeneic HCT could improve the effectiveness and quality of care overall for older patients with hematologic malignancies. The opposite could be true for younger but medically infirm patients by discouraging HCT for those who are unlikely to benefit from it while consuming extensive health resources.

The composite comorbidity/age index provided some information that could guide future research about suitability of given groups of patients to different intensities of conditioning regimens. Overall, results suggest that survival rates of patients with composite comorbidity/age scores of less than 3 are relatively good (> 60% at 2 years) and comparable among the three modalities of conditioning regimens. Therefore, patients with scores of less than 3 would be appropriate candidates for future clinical trials testing differences between conditioning intensities in survival as well as other outcomes such as quality of life or cost. One example is the current trial randomly assigning patients younger than age 66 years to either high-dose or reduced-intensity regimens (BMT CTN 0901; NCT01339910). HCT is now offered up to age 80 years at some centers, and with the continued expansion of the older patient population this trend is only expected to grow. The composite scores could be used to identify suitable older candidates for randomized trials comparing nonmyeloablative versus reduced-intensity regimens. Conversely, current results suggest that patients with composite scores of ≥ 3 seem to have survival benefits when offered nonmyeloablative versus high-dose regimens (HR, 0.72 for scores 3-4 and 0.73 for scores ≥ 5). However, patients with high scores did not benefit from receiving reduced-intensity versus high-dose regimens (HR, 0.99 for scores 3-4 and 0.86 for scores ≥ 5). In the future, the composite scores should be incorporated in the design of clinical trials that explore survival benefit of patients with high-risk comorbidities from novel reduced-intensity regimens with promising overall lower rates of NRM.

Death resulting from relapse typically constitutes half of the probability of failure of HCT. Here, we confirmed our previous observations regarding the predictive power of the HCT-CI for risks of

Table 4. Overall Mortality According to Conditioning Intensity Within Each Comorbidity/Age Risk Group

HCT-CI/Age Composite Score	Regimen		Overall 2-Year Survival (%)		Cox Regression Model*		
	Intensity	No. of Patients	Observed	Adjusted†	HR	95% CI	P
0 (n = 495)	High dose	417	79		1.0		
	Reduced intensity	40	87	83	0.76	0.3 to 1.7	.51
	Nonmyeloablative	38	81	85	0.72	0.4 to 1.5	.38
1-2 (n = 1,079)	High dose	737	66		1.0		
	Reduced intensity	130	66	70	0.79	0.6 to 1.1	.15
	Nonmyeloablative	212	67	74	0.89	0.7 to 1.1	.36
3-4 (n = 944)	High dose	499	45		1.0		
	Reduced intensity	178	47	50	0.99	0.8 to 1.3	.95
	Nonmyeloablative	267	54	59	0.72	0.6 to 0.9	.004
≥ 5 (n = 515)	High dose	236	29		1.0		
	Reduced intensity	117	34	35	0.86	0.6 to 1.1	.29
	Nonmyeloablative	162	35	37	0.73	0.6 to 1.0	.02

Abbreviations: ATG, antithymocyte globulin; CMV, cytomegalovirus; HCT-CI, hematopoietic cell transplantation–comorbidity index; HR, hazard ratio; KPS, Karnofsky performance status.

*The Cox regression models were adjusted for diagnosis category, disease risk, HCT-CI risk group, donor type, stem-cell source, KPS percentage, No. of prior regimens, use of ATG, and CMV serology status.

†Adjusted for patient characteristics of recipients of high-dose conditioning.

progression/relapse.³⁶ However, this predictive power remains limited compared with that for NRM (c-statistic estimate of 0.580 v 0.675, respectively, by the HCT-CI and 0.586 v 0.677, respectively, by the composite index). Accordingly, when using the composite comorbidity/age scores to estimate risks for mortality, physicians should weigh this information carefully against the burden and biologic behavior of the primary disease. Indeed, prediction of relapse is a relatively more complex task than that of NRM, given the different contributions of, for example, chromosomal, genetic, molecular, and other disease-specific abnormalities. Therefore, it would be best to use at least two separate models for risk assessment—one that captures biologic age for prediction of NRM and another that captures variable disease features^{1,37,38} for prediction of relapse and relapse-related mortality.

Although our observations might seem instinctive, it is true that, until now, assignment of patients to allogeneic HCT is based to a great extent on age, an observation that we challenge herein. Current results suggest that age is a poor prognostic marker and its use alone could be responsible for significant loss of life and/or resources. We propose a significant change in the practice of referral to allogeneic HCT where age is not to be considered alone for protocol criteria or treatment selection. Instead, all patients should be evaluated with the composite comorbidity/age score, summing the impact of comorbidities and age as well as appropriate features of their primary disease for selection of the most beneficial transplantation strategy. Regardless of age, patients with low scores should be considered for randomized clinical

trials or offered higher-intensity regimens. Likewise, regardless of age, patients with higher scores would be more suitable candidates for lower-intensity regimens. We believe this information would improve future knowledge of physicians and patients regarding effectiveness of medical interventions with the ultimate goal of improving outcomes and quality and reducing costs.³⁹

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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