

A Risk Score for Mortality after Allogeneic Hematopoietic Cell Transplantation

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Background: Despite recent advances, mortality rates after allogeneic hematopoietic cell transplantation remain high and cannot be accurately predicted.

Objective: To develop a reliable and valid predictor of all-cause mortality during the first 2 years after allogeneic hematopoietic cell transplantation.

Design: Retrospective cohort.

Setting: Tertiary hematopoietic cell transplantation center.

Patients: Patients ($n = 2802$) who received a first hematopoietic cell transplant between 1990 and 2002 were assigned to a development group or a validation group.

Measurements: Potential predictor variables were assessed with univariate and multivariable Cox proportional hazards methods to generate a prediction model. The c-statistic was calculated for 5 validation cohorts to assess model performance across early and late time periods and among patients with different diagnoses.

Results: The authors constructed a 50-point Pretransplantation Assessment of Mortality (PAM) score that incorporated 8 pretrans-

plantation clinical variables: patient age, donor type, disease risk, conditioning regimen, FEV₁, carbon monoxide diffusion capacity, serum creatinine level, and serum alanine aminotransferase concentration. The risk for death within 2 years for patients with PAM scores in the highest category was significantly higher than for those with scores in the lowest category. C-statistic values ranged from 0.69 to 0.76 for all validation cohorts.

Limitations: The predictor model was not validated in an external cohort and is only useful for predicting the risk for death within the first 2 years after hematopoietic cell transplantation.

Conclusions: Integrating pretransplantation clinical variables into a single score reliably predicts survival within 2 years after allogeneic hematopoietic cell transplantation. Accurate estimates of the risk for death may be useful in clinical trials and in epidemiologic studies. Such information can also be used to help physicians counsel patients regarding the expected outcomes of this potentially curative procedure.

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Hematopoietic cell transplantation (HCT) has become an important method of treating malignant conditions. The Center for International Blood and Marrow Transplant Research reported that approximately 16 000 patients throughout the world underwent allogeneic HCT in 2002. Despite trends showing improved outcomes after HCT, death after transplantation remains a major concern for these patients and their physicians. During the past decade, the overall mortality rate after allogeneic HCT improved modestly by 3% (1).

The risk for death after HCT depends on the underlying disease, the stage of the disease, and the type of donor (2, 3). However, the risk for post-transplantation death is also increased by such factors as higher exposures to total-body irradiation; certain methods of total-body irradiation delivery (4–6); and the presence of pulmonary, renal, or hepatic dysfunction before HCT (7–10). Although multivariable models have incorporated some of these conditions as risk factors for death, previous studies have not used these variables to predict this risk. The goal of this study was to develop a reliable and valid predictor of all-cause mortality during the first 2 years after allogeneic HCT. This assessment resulted in the development and validation of a 50-point integrated grading system that we have termed the Pretransplantation Assessment of Mortality (PAM) score.

METHODS

Patient Selection

This study was conducted by using clinical and laboratory data that were collected prospectively at the Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance, a tertiary cancer center that conducts an average of 350 to 400 allogeneic and autologous HCTs per year. Patients who underwent a first allogeneic HCT between 1 October 1990 and 31 December 2002 ($n = 3055$) were considered for this study. Patients who were younger than 15 years of age ($n = 219$) were excluded. Another 30 patients were excluded because their carbon monoxide diffusion capacity (DL_{CO}) was not assessed before transplantation, and 4 patients were excluded because their pretransplantation serum creatinine, total bilirubin, or serum alanine aminotransferase (ALT) levels were not available. The remaining 2802 patients were randomly divided

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Context

Many patients who undergo allogeneic hematopoietic cell transplantation have high mortality risks.

Contribution

In this retrospective cohort study involving 2802 patients with a first hematopoietic cell transplant, investigators devised a 50-point pretransplantation score that predicted risk for death within 2 years. Score variables included age, donor type, disease type, conditioning regimen, FEV₁, carbon monoxide diffusion capacity, serum creatinine level, and serum alanine aminotransferase concentration.

Cautions

We recommend validation of this prognostic score in other populations and settings before routine use.

—The Editors

into 2 groups: a development group ($n = 1401$) and a validation group ($n = 1401$). We decided a priori to further subdivide the validation cohort into 2 subgroups to account for changes in HCT practice across time: an early validation subgroup ($n = 853$), which comprised patients who underwent HCT between 1 October 1990 and 31 December 1997, and a late validation subgroup ($n = 548$), which comprised patients who underwent HCT between 1 January 1998 and 31 December 2002. The cutoff point was set at the end of 1997 because nonmyeloablative transplant protocols were initiated at our center in 1998.

Clinical Variables

We defined potential 2-year mortality risk factors as demographic, clinical, and laboratory data that were known to be associated with higher mortality risk and were routinely available during a standard pretransplantation assessment. In addition to their relationship to death risk, these variables were selected because they were likely to be available to physicians outside our center and because they were likely to minimize variation in interpretation of the data, to maximize the general applicability of this scoring system, and to maximize its reproducibility in performance.

Because of the large number of heterogeneous diagnoses and stages of disease, we simplified disease risk categories by ranking them according to the outcomes that we observed at our center. Low-risk diseases included chronic myelogenous leukemia in chronic phase, refractory anemia, aplastic anemia, and the Blackfan–Diamond syndrome. Intermediate-risk diseases included chronic myelogenous leukemia in accelerated phase or in 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 chronic myelogenous leukemia in blastic phase, juvenile chronic myelogenous leukemia, acute leu-

kemia or lymphoma in relapse, refractory anemia with excess blasts in transformation, and myeloma. Solid tumors and nonhematologic diseases were also classified as high-risk diseases.

Stem-cell sources were classified as bone marrow; growth factor–mobilized blood cells; or other, which included cord blood or a combination of bone marrow and mobilized blood cells. Matching between the donor and recipient was determined according to donor–recipient HLA-A, HLA-B, and HLA-DR compatibility. Conditioning regimens were first grouped according to myeloablative or nonmyeloablative categories. Myeloablative regimens were categorized according to the dose of total-body irradiation used (≤ 12 Gy or > 12 Gy). All patients in the nonmyeloablative group received 2 Gy of total-body irradiation.

All pulmonary function tests were performed at our center according to American Thoracic Society guidelines (11–13). We assessed FEV₁ and DL_{CO}, which was adjusted for the most recently documented hemoglobin level, because these studies were previously identified in multivariable models to be significantly associated with increased mortality risk after transplantation (7). All pulmonary function values were expressed as a percentage of the predicted values that were calculated according to published equations (14, 15). Serologic studies for cytomegalovirus infection were performed. We used measurements of serum creatinine, total bilirubin, and ALT levels that were obtained most recently before the conditioning regimen was initiated. By using our center’s laboratory standards, we classified the following results as abnormal: serum creatinine level greater than 110 $\mu\text{mol/L}$ (> 1.2 mg/dL), serum total bilirubin level greater than 22 $\mu\text{mol/L}$ (1.3 mg/dL), and serum ALT level greater than 49 U/L.

The primary outcome was death (regardless of cause) within the first 2 years after transplantation. All patients were followed for at least 2 years after the procedure or until death. We contacted patients, their primary care physicians, or their oncologists by telephone at least 1 time per year as part of routine post-transplantation protocol.

Statistical Analysis

All statistical analyses were performed by using Stata software, version 8.0 (Stata Corp., College Station, Texas). All potential risk factors were considered to be categorical variables. The Pearson chi-square test was used for all univariate analyses. Cox proportional hazards regression models were used to conduct a survival (time-to-death) analysis. The Schoenfeld residual test was used to evaluate model fit and the tenability of the proportional hazards assumption for all Cox proportional hazards regression models. All patients were followed until death or were censored at the end of the 2-year follow-up period. Statistical significance was defined as a 2-sided P value of less than 0.1 in univariate analyses for covariate selection and as a 2-sided P value of less than 0.05 in multivariable analyses.

Development of the PAM Score

The development cohort was used to construct the PAM score. All clinical variables were first assessed for their association with 2-year survival in univariate analysis. Variables found to be associated with 2-year survival at a statistically significant threshold ($P < 0.1$) were assessed in a multivariable Cox proportional hazards model. We used a

stepwise selection algorithm, retaining in the final model only those variables that contained at least 1 statistically significant category ($P < 0.05$). To create an easily applicable scoring system, we multiplied the β coefficients from the final model by 10 and rounded the values to the nearest integer. The sum of these integer weights was used as a simplified scoring scheme.

Table 1. Univariate and Multivariable Analyses for the Development of the Pretransplantation Assessment of Mortality Score*

Variable	Patients, n (%)	Deaths, n	P Value	Multivariate Hazard Ratio for Death (95% CI)	P Value	β Value	Score†
Age							
<20 y	65 (5)	34	<0.001	Referent	–	–	1
20–30 y	214 (15)	99		0.84 (0.56–1.25)	0.39	0.1	1
30–40 y	380 (27)	159		0.86 (0.59–1.25)	0.44	0.1	1
40–50 y	423 (30)	208		1.08 (0.75–1.56)	0.68	0.1	1
50–60 y	271 (19)	153		1.39 (0.95–2.05)	0.090	0.3	3
>60 y	48 (4)	35		1.72 (1.04–2.84)	0.036	0.5	5
Sex of recipient							
Male	822 (59)	425	0.021	–	–	–	–
Female	579 (41)	263		–	–	–	–
Sex of donor							
Male	799 (57)	391	0.81	–	–	–	–
Female	602 (43)	297		–	–	–	–
Recipient/donor sexes							
Female/female	273 (20)	121	0.097	–	–	–	–
Female/male	306 (22)	142		–	–	–	–
Male/male	493 (35)	249		–	–	–	–
Male/female	329 (23)	176		–	–	–	–
Donor type							
Related, matched	663 (47)	290	<0.001	Referent	–	–	1
Unrelated	596 (43)	305		1.40 (1.18–1.66)	<0.001	0.3	3
Related, mismatched	142 (10)	93		1.57 (1.23–2.00)	<0.001	0.4	4
Disease risk							
Low	392 (28)	90	<0.001	Referent	–	–	1
Intermediate	390 (28)	204		2.31 (1.77–3.03)	<0.001	0.8	8
High	619 (44)	394		3.41 (2.66–4.37)	<0.001	1.2	12
Stem cell sources							
Bone marrow	1059 (76)	507	0.22	–	–	–	–
Peripheral blood stem cells	329 (23)	172		–	–	–	–
Cord, bone marrow, and/or peripheral blood stem cells	13 (1)	9		–	–	–	–
Cytomegalovirus status (recipient/donor)							
Negative/negative	468 (33)	208	0.026	–	–	–	–
Negative/positive	209 (15)	111		–	–	–	–
Positive/negative	312 (22)	169		–	–	–	–
Positive/positive	412 (30)	200		–	–	–	–
Conditioning regimens							
Nonmyeloablative	87 (6)	49	<0.001	Referent	–	–	1
Non-total-body irradiation	448 (32)	177		1.52 (1.06–2.17)	0.022	0.4	4
Total-body irradiation with ≤ 12 Gy	386 (28)	169		2.18 (1.51–3.15)	<0.001	0.8	8
Total-body irradiation with > 12 Gy	480 (34)	293		2.48 (1.72–3.57)	<0.001	0.9	9
Serum creatinine level							
$\leq 106 \mu\text{mol/L}$ ($\leq 1.2 \text{ mg/dL}$)	1268 (90)	595	<0.001	Referent	–	–	1
$> 106 \mu\text{mol/L}$ ($> 1.2 \text{ mg/dL}$)	133 (10)	93		2.28 (1.63–3.19)	<0.001	0.8	8
Serum total bilirubin level							
$\leq 22 \mu\text{mol/L}$ ($\leq 1.3 \text{ mg/dL}$)	1309 (93)	627	0.001	–	–	–	–
$> 22 \mu\text{mol/L}$ ($> 1.3 \text{ mg/dL}$)	92 (7)	61		–	–	–	–
Serum alanine aminotransferase level							
$\leq 49 \text{ U/L}$	1092 (78)	512	0.002	Referent	–	–	1
$> 49 \text{ U/L}$	309 (22)	176		1.25 (1.05–1.49)	0.011	0.2	2
FEV₁							
$> 80\%$	1158 (83)	527	<0.001	Referent	–	–	1
70%–80%	158 (11)	96		1.31 (1.05–1.64)	0.019	0.3	3
$< 70\%$	85 (6)	65		1.88 (1.42–2.49)	<0.001	0.6	6
Carbon monoxide diffusing capacity							
$> 80\%$	1183 (84)	550	<0.001	Referent	–	–	1
70%–80%	138 (10)	80		1.08 (0.84–1.38)	0.56	0.1	1
$< 70\%$	80 (6)	58		1.55 (1.16–2.07)	0.003	0.4	4

* Multivariable data are not shown for variables not significant in the final model.
 † Score is determined by multiplying the β value by 10.

Table 2. Distribution and Comparison of the Variables in the Pretransplantation Assessment of Mortality Score in Validation and Diagnostic Subgroups

Variable	Validation Group, n (%)		P Value†	Diagnostic Subgroup, n (%)*		
	Early (n = 853)	Late (n = 548)		Chronic Myelogenous Leukemia (n = 1017)	Acute Myelogenous Leukemia (n = 667)	Myelodysplastic Syndrome (n = 407)
Age			<0.001			
<20 y	61 (7)	28 (5)		35 (4)	40 (6)	10 (2)
20–30 y	156 (18)	47 (9)		149 (15)	108 (16)	23 (6)
30–40 y	228 (27)	123 (22)		336 (33)	167 (25)	74 (18)
40–50 y	249 (29)	174 (32)		318 (31)	198 (30)	124 (31)
50–60 y	151 (18)	132 (24)		165 (16)	128 (19)	134 (33)
>60 y	8 (1)	44 (8)		14 (1)	26 (4)	42 (10)
Donor type			<0.001			
Related, matched	412 (48)	281 (51)		386 (38)	329 (49)	201 (49)
Unrelated	318 (37)	247 (45)		520 (51)	259 (39)	175 (43)
Related, mismatched	123 (15)	20 (4)		111 (11)	79 (12)	31 (8)
Disease risk			0.004			
Low	256 (30)	133 (24)		716 (70)	–	2 (1)
Intermediate	216 (25)	181 (33)		229 (23)	329 (49)	9 (2)
High	381 (45)	234 (43)		72 (7)	338 (51)	396 (97)
Conditioning regimen			<0.001			
Nonmyeloablative	0	87 (16)		16 (2)	39 (6)	19 (5)
Non-total-body irradiation	270 (32)	209 (38)		317 (31)	152 (23)	262 (64)
Total-body irradiation with ≤12 Gy	201 (23)	139 (25)		379 (37)	148 (22)	97 (24)
Total-body irradiation with >12 Gy	382 (45)	113 (21)		305 (30)	328 (49)	29 (7)
FEV₁			0.85			
>80%	690 (81)	445 (81)		889 (87)	542 (81)	323 (80)
70%–80%	102 (12)	61 (11)		87 (9)	83 (13)	50 (12)
<70%	61 (7)	42 (8)		41 (4)	42 (6)	34 (8)
Carbon monoxide diffusing capacity			0.007			
>80%	681 (80)	469 (86)		913 (90)	530 (80)	353 (87)
70%–80%	99 (12)	54 (10)		70 (7)	83 (12)	36 (9)
<70%	73 (8)	25 (4)		34 (3)	54 (8)	18 (4)
Serum alanine aminotransferase level			0.110			
≤49 U/L	669 (78)	449 (82)		866 (85)	495 (74)	312 (77)
>49 U/L	184 (22)	99 (18)		151 (15)	172 (26)	95 (23)
Serum creatinine level			0.86			
≤106 μmol/L (≤1.2 mg/dL)	768 (90)	495 (90)		964 (95)	597 (90)	367 (90)
>106 μmol/L (>1.2 mg/dL)	85 (10)	53 (10)		53 (5)	70 (10)	40 (10)

* Diagnostic subgroups were identified after combining all patients in the development and validation groups.
 † P values refer to comparison between early and late validation groups.

Validation of PAM Scores

We divided the distribution of PAM scores into 4 categories according to the probability of death in the development cohort: category 1, less than 25%; category 2, 25% to 50%; category 3, 50% to 75%; and category 4, greater than 75%. To assess the discriminatory capability of the PAM score for 2-year survival, we computed the c-statistic. In the case of a binary outcome, such as survival, the c-statistic was interpretable as the area under a receiver-operating characteristic curve for comparing predictions in 2 outcome groups (16). We also graphically compared survival functions by using Kaplan–Meier survival curves to assess model fit. To make these assessments, we used both the early and the late validation cohorts and subgroups of patients with the 3 diseases observed most commonly in our entire study sample: chronic myelogenous leukemia (n = 1017), acute myelogenous leukemia (n = 667), and the myelodysplastic syndrome (n = 407).

Role of the Funding Sources

The funding sources, the American Lung Association and the National Marrow Donor Program, had no role in the design, conduct, or analysis of this study or in the decision to submit the manuscript for publication.

RESULTS

Development of the PAM Score

The overall 2-year mortality rate for the development cohort was 49%. Of the 14 clinical variables initially selected, 11 were statistically significant (P < 0.1) in univariate analysis and were considered in multivariable analysis (Table 1). Multivariable analysis retained 8 statistically significant (P < 0.05) clinical variables: age, donor type, disease risk, conditioning regimen, percentage of predicted FEV₁, percentage of predicted DL_{CO}, serum creatinine level, and serum ALT level (Table 1).

By using this model, we gave a score to each patient in the development cohort. For example, a 45-year-old patient who had chronic myelogenous leukemia in accelerated phase was to receive a myeloablative transplant from an unrelated donor. The patient had a pretransplantation FEV₁ that was 75% of predicted, DL_{CO} that was 95% of predicted, serum creatinine level of 130 μmol/L (1.5 mg/dL), and serum ALT level of 110 U/L; he was scheduled to receive 12 Gy of total-body irradiation. On the basis of these data, the patient received a PAM score of 34 (1 + 8 + 3 + 1 + 8 + 2 + 8 + 3). We generated 4 categories of PAM scores by setting cutoffs according to the probability of death. Scores ranged from 9 to 16 for category 1 (probability of death, <25%), from 17 to 23 for category 2 (probability of death, 25% to 50%), from 24 to 30 for category 3 (probability of death, 50% to 75%), and from 31 to 44 for category 4 (probability of death, >75%).

Validation of PAM Scores

The 2-year mortality rate for the entire validation cohort was 51%. The PAM scores for the group ranged from 9 to 44 and were normally distributed; the mean score was 23.73 (SD, 6.41). The 2-year mortality rates for the early and late validation subgroups were 53% and 48%, respectively. For the early validation subgroup, PAM scores ranged from 11 to 44 with a mean score of 24.20 (SD,

6.65); for the late validation subgroup, scores ranged from 9 to 42 with a mean score of 23.0 (SD, 5.95). The latter group included older patients and more patients who received transplants from unrelated donors; more of the patients in this group received low-intensity (2-Gy) nonmyeloablative conditioning regimens or myeloablative regimens that did not require total-body irradiation. Pretransplantation DL_{CO} values in the late validation group were also higher (Table 2).

Despite these differences, the risk for death for patients in each of the PAM score categories was similar. Higher PAM scores were associated with progressively increased risk for death (Table 3). The mortality risk was high for patients in category 4 of the late validation cohort because category 1, the reference group, had very few patients (*n* = 5). When category 2 was used as the reference group, the hazard ratio was 1.82 (95% CI, 1.37 to 2.42) for category 3 and 3.75 (CI, 2.46 to 5.71) for category 4. Because no patients in category 1 of the acute myelogenous leukemia and myelodysplastic syndrome groups had a PAM score within the range of 9 to 16, this category was not used as a reference group; therefore, the risk was lower for category 4. However, the risk was proportionally similar to that observed for the early and late validation cohorts and for the chronic myelogenous leukemia cohort.

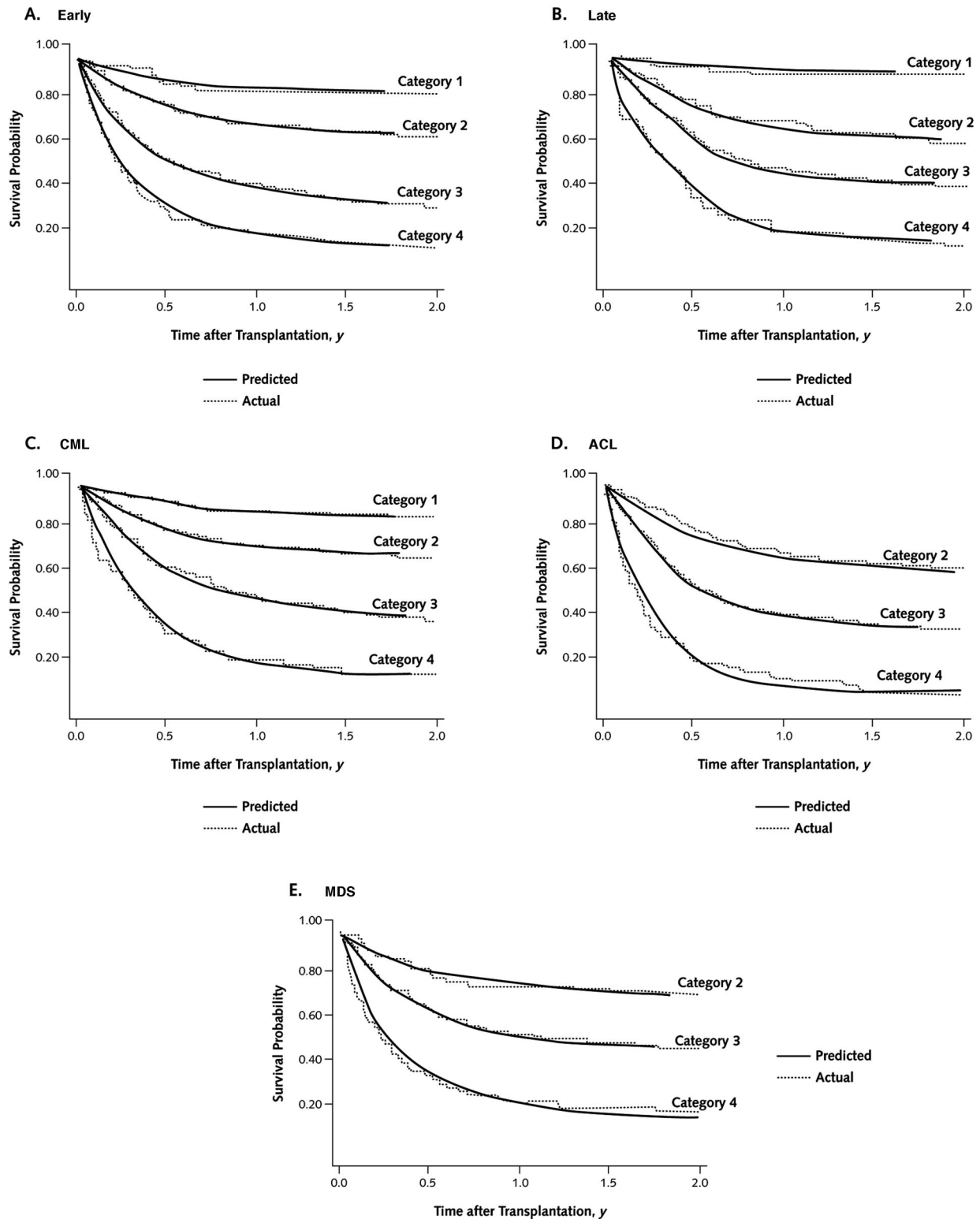
Table 3. Hazard Ratios Associated with the Pretransplantation Assessment of Mortality Score for the Early and Late Validation Groups and Three Disease Subgroups*

Score Category	Patients, <i>n</i>	Deaths, <i>n</i> (%)	Hazard Ratio (95% CI)
Early validation group			
Category 1 (score of 9–16)	92	15 (16)	Referent
Category 2 (score of 17–23)	267	93 (35)	2.39 (1.38–4.12)
Category 3 (score of 24–30)	365	240 (66)	5.89 (3.49–9.91)
Category 4 (score of 31–44)	129	105 (81)	10.26 (5.96–17.65)
Late validation group			
Category 1 (score of 9–16)	63	5 (8)	Referent
Category 2 (score of 17–23)	182	70 (38)	5.72 (2.31–14.18)
Category 3 (score of 24–30)	264	153 (58)	10.41 (4.27–25.37)
Category 4 (score of 31–42)	39	32 (82)	21.39 (8.32–54.98)
Chronic myelogenous leukemia group			
Category 1 (score of 9–16)	285	40 (14)	Referent
Category 2 (score of 17–23)	479	151 (32)	2.54 (1.79–3.60)
Category 3 (score of 24–30)	213	127 (60)	5.80 (4.06–8.28)
Category 4 (score of 31–44)	40	33 (83)	12.00 (7.55–19.08)
Acute myelogenous leukemia group			
Category 1 (score of 9–16)	0	0	–†
Category 2 (score of 17–23)	170	66 (39)	Referent
Category 3 (score of 24–30)	383	249 (65)	2.21 (1.68–2.90)
Category 4 (score of 31–43)	114	103 (90)	5.56 (4.07–7.61)
Myelodysplastic syndrome			
Category 1 (score of 9–16)	1	0	–†
Category 2 (score of 17–23)	63	17 (27)	Referent
Category 3 (score of 24–30)	288	149 (52)	2.29 (1.38–3.78)
Category 4 (score of 31–43)	55	43 (78)	5.34 (3.04–9.38)

* All *P* values are less than 0.001.

† Category 1 was excluded from the Cox proportional hazards model because there were no patients in this category.

Figure. Assessment of model fit.



The actual Kaplan–Meier survival curves of the early and late validation cohorts and for the 3 most common disease categories (chronic myelogenous leukemia [CML], acute myelogenous leukemia [AML], and the myelodysplastic syndrome [MDS]) were compared with the Pretransplantation Assessment of Mortality (PAM) score–predicted survival curves as calculated by the Cox proportional hazards model. The category 1 curves were excluded from the acute myelogenous leukemia and myelodysplastic syndrome graphs because there were no patients in those respective quartiles. Near superimposition of the actual and predicted survival curves indicates that the PAM model fits the 5 cohorts well.

The fit of the PAM score model was assessed by graphically comparing the predicted and actual survival among the early and late validation cohorts and the disease subgroups (Figure). These plots demonstrated close approximation of the predicted and actual curves, suggesting that the PAM score model did not overfit the data in these cohorts. The PAM score performed similarly in discriminating 2-year risk for death after transplantation for each cohort. The *c*-statistic was 0.76 for the early validation group, 0.72 for the late validation group, 0.75 for the chronic myelogenous leukemia group, 0.72 for the acute myelogenous leukemia group, and 0.69 for the myelodysplastic syndrome group.

DISCUSSION

Patients who are candidates for allogeneic HCT represent a specialized population at high risk for death. Although several independent risk factors have been previously shown to be associated with increased mortality rates, their performance as clinical predictors of death has not been assessed in an integrated fashion. Some of the 8 variables that we identified as important were previously recognized as independent risk factors for death related to relapse or transplantation. Integration of these variables into a single model demonstrates the relative importance of these pretransplantation variables. When examined together, these variables probably provide a comprehensive preliminary assessment of risk for post-transplantation complications, such as graft-versus-host disease, opportunistic infections, and severe pulmonary syndromes, all of which are well-known causes of death after HCT.

The applicability of a prognostic system is demonstrated primarily by its performance and validation in different patient populations. Our study validated the PAM score as a predictor of mortality risk in 2 separate subsets of a validation cohort with substantially different characteristics. Despite these differences, the PAM score performed equally well in predicting the 2-year mortality risk. Of particular interest was the late validation cohort, which contained patients who received a low-intensity (2-Gy) nonmyeloablative conditioning regimen that is now used for approximately 40% of patients who undergo allogeneic HCT at our center. We also demonstrated that the PAM score performed well when applied to the most common disease subgroups at our institution. This finding suggests that the PAM score could be used for most patients who are considering an allogeneic HCT regardless of the underlying diagnosis, provided that information is available to determine the appropriate disease risk category.

Our study has several limitations. First, it would have benefited from external validation at an independent transplantation center. For example, the categorization of disease risk was based on our institution's experience and may not apply to other transplantation centers. Ideal resources for validation data include the National Marrow Donor

Program and the Center for International Blood and Marrow Transplant Research. Unfortunately, neither program routinely tracks pulmonary function data before transplantation. However, the overall 2-year mortality rate for patients at our center is similar to results from centers in Europe (17), suggesting that our patient cohort may not be too different from other HCT cohorts.

Second, we assessed mortality rates only within the first 2 years after HCT. Differences in survival probability among patients within the PAM score categories were greater during the first year after HCT and were somewhat less apparent during the second year. Consequently, the risk factors in our model seem to be most useful for predicting the risk for early death after HCT.

Third, our study did not explicitly consider other comorbid conditions that are associated with increased risk for death in general medical populations. Patients with advanced coexisting illnesses often do not meet transplant eligibility criteria, and our experience suggests that such coexisting conditions are not commonly encountered in this population. A recent study demonstrated that 88% of patients receiving a myeloablative conditioning regimen had a Charlson Comorbidity Index score of 0 (excluding hematologic cancer) (18). However, patients who undergo HCT do have some comorbid conditions; consequently, researchers have developed an HCT-specific index for assessing comorbid conditions (19), a tool that requires the gathering and analysis of data for 17 clinical variables that are highly specific for this population. Because the PAM score does not capture comorbid information that is specific to the population of patients who have undergone HCT, it is unable to provide any information regarding how comorbid conditions might influence the mortality risk. However, as a tool for predicting a patient's survival probability (its intended purpose), the PAM score performs well. Furthermore, the PAM scoring system requires information for only 8 clinical variables, all of which are generally monitored at most transplantation centers. These requirements make the PAM score simple to use and will hopefully increase the likelihood that it will be applied in a clinical setting. To further improve the practical application of our system, we have developed a PAM score calculator that can be easily accessed through the Internet at <http://cdsweb.fhcrc.org/pam/>.

Fourth, the results of our study are limited to patients who underwent HCT at our center and did not include those who did not qualify for the procedure, those who had the procedure at another center, or those who elected not to undergo the procedure despite meeting the requirements for transplantation. In addition, future consideration of PAM scores in decisions to undergo HCT could alter the distribution of scores among patients who have the procedure. Furthermore, transplantation practice is continually changing, as evidenced by the increasing use of reduced-intensity conditioning regimens. Therefore, future evaluations would be needed to reassess the PAM score's

continued validity, as would be the case for any predictive index.

In conclusion, we present the development and validation of a simple tool for predicting mortality risk in patients who are considering allogeneic HCT. We believe the PAM score can serve 2 useful purposes. First, oncologists and primary care physicians could use this straightforward algorithm to help patients better appreciate their risk for death after HCT and to improve patient understanding of characteristics that influence this risk. Accurate assessment of mortality risk in patients who are considering HCT may enhance their participation during discussion of the risks and benefits of this dangerous but potentially curative procedure. Second, clinical investigators may find the PAM score useful as a simple global tool for assessing mortality risk when designing clinical trials and analyzing transplantation outcomes data. Future studies will be necessary for assessing the validity of the PAM score outside our center.

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