Chronic GVHD risk score: a Center for International Blood and Marrow Transplant Research analysis

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Several risk factors are associated with increased mortality in patients with chronic graft-versus-host disease (cGVHD), but there is considerable variability in the reported factors. Therefore, we evaluated patient, transplantation, and cGVHD characteristics to develop a risk score in 5343 patients with cGVHD. Ten variables were identified as being significant in multivariate analysis of overall survival and nonrelapse mortality (NRM): age, prior acute GVHD, time from transplantation to cGVHD, donor type, disease status at transplantation, GVHD prophylaxis, gender mismatch, serum bilirubin, Karnofsky score, and platelet count. These 10 variables were used to build a cGVHD risk score, and 6 risk groups (RGs) were identified. The 5-year NRM was 5% (1%-9%) in RG1, 20% (19%-23%) in RG2, 33% (29%-37%) in RG3, 43% (40%-46%) in RG4, 63% (53%-74%) in RG5, and 72% (59%-85%) in RG6. The 5-year overall survival was highest at 91% (95% confidence interval [CI]:85%-97%) in RG1, followed by 67% (65%-69%) in RG2, 51% (46%-55%) in RG3, 40% (37%-43%) in RG4, 21% (12%-30%) in RG5, and 4% (0%-9%) in RG6 (all $P < .01$). This analysis demonstrates the usefulness of data from a large registry to develop risk-score categories for major transplantation outcomes. Validation of this cGVHD risk score is needed in a different population to ensure its broad applicability. (*Blood*. 2011;117(24):6714-6720)

Introduction

Chronic graft-versus-host disease (cGVHD) is the leading cause of late morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT).[1,2] Several risk factors predicting survival in patients with cGVHD have been reported.[3-11] These include recipient and donor age,[11] lichenoid skin changes,[10] > 50% body surface area of skin involvement,[4] elevated bilirubin,[10] progressive onset of cGVHD,[10] thrombocytopenia,[4,5,9] gut involvement,[5,7] Karnofsky performance status (KPS)/Lansky status,[7] still receiving corticosteroids at the time of cGVHD diagnosis,[11] HLA mismatch,[11] and absence of early response to immunosuppression.[5] Of these, the most consistent factors across studies remains thrombocytopenia at diagnosis of cGVHD and progressive onset of disease, with studies reporting variability in the other factors reported. We proposed to identify a simple model using readily available patient, disease, and HCT characteristics in conjunction with objective variables at diagnosis of cGVHD (thrombocytopenia, serum bilirubin, KPS, time to onset of cGVHD, and type of onset of cGVHD) to develop a risk score in a cohort of 5343 patients with cGVHD who registered with the Center for International Blood and Marrow Transplant Research (CIBMTR). We hypothesized that the development of a simple cGVHD risk score using the largest available multicenter cohort could lead to better generalizability and easier identification of high-risk populations for therapeutic trials or clinical use. Therefore, in the current study, we evaluated this cohort of patients with cGVHD for overall survival and nonrelapse mortality (NRM) and incorporated multiple variables to develop a new risk-score model that predicts overall survival and NRM for patients with cGVHD.

Methods

The CIBMTR is a research organization formed in 2004 as an affiliation of the International Bone Marrow Transplant Registry (IBMTR), the Autologous Blood and Marrow Transplant Registry (ABMTR), and the National

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Marrow Donor Program (NMDP). The CIBMTR is a voluntary organization involving more than 500 transplantation centers that have collaborated to share patient data and conduct scientific studies. The quality and compliance of data submission are monitored by computerized checks for errors, physician reviews, and on-site audits.

Patient selection

Our study population included all patients who received an allogeneic hematopoietic cell transplantation (HCT) from a related or unrelated donor (URD) including umbilical cord blood for acute myelogenous leukemia, acute lymphoblastic leukemia, chronic myelogenous leukemia, or myelodysplastic disorders between 1995 and 2004; were diagnosed with cGVHD within 1 year of transplantation; and were registered with CIBMTR. All surviving recipients who received transplantations from URDs included in this analysis were retrospectively contacted and provided informed consent for participation in the NMDP research program. Informed consent for retrospective data analysis was waived by the NMDP institutional review board for all deceased patients. Surviving patients who did not provide signed informed consent to allow analysis of their clinical data were excluded. To adjust for potential bias introduced by the exclusion of nonconsenting surviving patients, a corrective action plan modeling process randomly excluded approximately the same percentage of deceased patients using a biased coin randomization with exclusion probabilities based on characteristics associated with not providing consent for use of data in survivors. The study included a total of 5343 HCT recipients with cGVHD.

Study end points and definitions

The primary end points of the study were overall survival and NRM. Predictive factors significant in the model for overall survival were used to develop a risk score for recipients with cGVHD. Overall survival was estimated from the onset of cGVHD. Death from any cause was treated as the event. Surviving patients were censored at the date of last contact. NRM was defined as death in continuous remission. The event was summarized by the cumulative incidence estimate with relapse as the competing risk. Grade II-IV acute GVHD was graded according to IBMTR criteria based on the pattern of severity of abnormalities in the skin, gastrointestinal tract, and liver.[12] cGVHD was diagnosed according to standard CIBMTR criteria,[7,13] which includes all patients with clinical criteria of cGVHD[13] with or without positive histology, irrespective of time of onset of symptoms. Data required to generate an National Institutes of Health (NIH) score were not prospectively collected by the CIBMTR during the study period.[14] We defined reduced intensity/nonmyeloablative regimens as follows: busulfan dose < 9 mg/kg, melphalan dose < 150 mg/m^2, and total body irradiation dose < 500 cGy (single or fractionated) or 500-800 cGy (fractionated).[15]

Statistical analysis

Variables related to patient, disease, and transplantation characteristics were described using descriptive statistics. Cumulative incidence for NRM was calculated treating disease progression/relapse as the competing risk.[16] Overall survival was calculated using Kaplan-Meier estimates, and 95% confidence intervals (CIs) were calculated using the variance derived from the formula of Greenwood.[17] We used the log-rank test to compare the differences between groups in the time-to-event analyses. All P values were 2-sided.

Patient-, disease-, transplant-, and cGVHD-related variables were included in the multivariate analyses using a stepwise forward selection technique. $P \leq .01$ was the criterion for inclusion in the final models.[18] Patient and transplantation-related variables included were: recipient age, donor type (HLA-matched sibling donor vs other related donor vs well-matched URD vs partially matched URD vs mismatched URD), graft type (bone marrow, peripheral blood, or umbilical cord blood), donor-recipient sex mismatch, donor-recipient cytomegalovirus serology, conditioning regimen (ablative vs reduced intensity conditioning/nonmyeloablative), GVHD prophylaxis, presence of prior acute GVHD, and grade and year of transplantation. Disease-related variables included diagnosis and disease status before transplantation. cGVHD-related variables included time from HCT to cGVHD onset, platelet count at cGVHD diagnosis ($< 100 \times 10^9$/L vs $> 100 \times 10^9$/L), serum bilirubin at cGVHD onset (< 1 mg/dL, 1-2 mg/dL, or > 2 mg/dL), type of onset of cGVHD (progressive, quiescent, or de novo), and KPS at diagnosis of cGVHD. These cGVHD-related variables were chosen because they are objective, simple to use, and available at the time of diagnosis. Organ involvement was not considered because cGVHD may progress to involve more organs. The CIBMTR collects cGVHD data over a time period of 100 days, 6 months, and 1 year after transplantation for patients registered with the NMDP, and at 6 months and 1 year for patients registered with the IBMTR. Forms report the maximum organ involvement in the preceding time interval, which may represent disease that had progressed since diagnosis. Analysis methodology for development of risk score is discussed with the results.

Results

Patient characteristics

The study cohort included 5343 recipients with cGVHD. Table 1 demonstrates the patient-, disease-, transplantation-, and cGVHD-related variables for these recipients. The median age at HCT was 36 years (range $<$ 1-72). The majority (55%) received HCT for acute leukemia, 34% for chronic myelogenous leukemia, and 11% for myelodysplastic disorders. The majority received transplantation in early disease status (55%). Thirty (7%) received HCT from an HLA-identical sibling donor, 4% from other related donors, and 54% from a URD (including 127 recipients of unrelated umbilical cord blood). Among the cGVHD-related variables, the median time from transplantation to cGVHD onset was 5 months (range 1-11 months), 43% had progressive onset of disease, and 36% had a platelet count of $< 100 \times 10^9$/L at diagnosis.

Overall survival

The probability of overall survival was 72% (95% CI 71%-73%) at 1 year and 55% (95% CI 54%-57%) at 5 years. In the multiple-regression model, increasing recipient age, the presence of and higher grade of prior acute GVHD, early onset of cGVHD (< 5 months), higher serum bilirubin at cGVHD onset, lower KPS at cGVHD onset, presence of thrombocytopenia at cGVHD onset (platelet count of $< 100 \times 10^9$/L), transplantation from a mismatched URD or other related donor versus an HLA-identical sibling donor, disease status at transplantation (intermediate or advanced versus early), GVHD prophylaxis, and gender mismatch (female donor to male recipient versus male donor to male recipient) were significantly associated with a higher risk of mortality (Table 2).

NRM

The cumulative incidence of NRM was 21% (95% CI 20%-22%) at 1 year and 31% (95% CI 29%-32%) at 5 years. In the multiple-regression model, the same factors identified for overall survival were also identified to be predictive of NRM (Table 2). Because patients with progressive onset of cGVHD were identified to have an earlier time to onset (median 3.6 months) compared with de novo (median 5.2 months) and quiescent (median 5.5 months) cGVHD, the relationship between time to onset and type of onset was evaluated and found to be nonsignificant.

Table 1. Patient and transplantation characteristics

Characteristics	n (%)
Number of patients	5343
Number of centers	286
Age at transplantation, y	
Median (range)	36 (< 1-72)
0-9	451 (8)
10-19	665 (12)
20-29	906 (17)
30-39	1207 (23)
40-49	1212 (23)
50-59	742 (14)
≥ 60	160 (3)
Male sex	3182 (60)
Disease	
AML	1802 (34)
ALL	1140 (21)
CML	1813 (34)
MDS	588 (11)
Disease status before transplantation*	
Early	2956 (55)
Intermediate	1367 (26)
Advanced	1020 (19)
Graft source	
Bone marrow	3302 (62)
Peripheral blood	1914 (36)
Umbilical cord blood	127(2)
HLA-matching status†	
HLA-identical sibling	1968 (37)
Other related	226 (4)
Well-matched unrelated	1261 (24)
Partially matched unrelated	1060 (20)
Mismatched unrelated	532 (10)
Missing HLA data	296 (6)
Conditioning regimen	
Myeloablative	4749 (89)
Reduced intensity/nonmyeloablative	594 (11)
Donor-recipient gender match	
Male donor → male recipient	1804 (34)
Male donor → female recipient	1105 (21)
Female donor → male recipient	1378 (26)
Female donor → female recipient	1056 (20)
Donor-recipient CMV match	
Donor(−)/recipient(−)	1561 (29)
Donor(−)/recipient(+)	1140 (21)
Donor(+)/recipient(−)	697 (13)
Donor(+)/recipient(+)	1688 (32)
Unknown	257 (5)
GVHD prophylaxis	
T-cell depletion	1242 (23)
CSA ± MTX ± other	3341 (63)
FK506 ± MTX ± other	760 (14)
Year of transplantation	
1995-1999	2742 (51)
2000-2004	2601 (49)
Grade of acute GHVD	
None	1433 (27)
I-II	2258 (42)
III-IV	1652 (31)
Time from transplantation to cGHVD, mo (range)	5 (1-11)
Onset of cGVHD	
Progressive	2301 (43)
Quiescent	1430 (27)
De novo	1433 (27)
Missing	179 (3)
Maximum grade of cGVHD	
Limited	1707 (32)
Extensive	3636 (68)
Karnofsky score at diagnosis of cGVHD	
< 80	1570 (29)
80-100	3007 (56)
Unknown	766 (14)
Platelet count at cGVHD, × $10^{9/L}$	
Median (range)	117 (< 1-718)
< 100	1921 (36)
≥ 100	2650 (50)
Missing	772 (14)
Serum bilirubin at cGVHD, mg/dL	
Median (range)	1 (< 1-98)
< 1	2928 (55)
1-2	982 (18)
> 2	925 (17)
Missing	508 (10)
Duration of immunosuppression	
< 1 y	1953 (37)
1-2 y	650 (12)
2-3 y	404 (8)
3-4 y	371 (7)
> 4 y	1007 (19)
Missing	958 (18)
Median follow-up of survivors, mo	73 (3-168)

AML indicates acute myeloid leukemia; ALL, acute lymphoid leukemia; CML, chronic myeloid leukemia; CMV, cytomegalovirus; MDS, myelodysplastic syndrome; CSA, cyclosporine, and MTX, methotrexate, FK506:tacrolimus.

*Disease status before transplantation was defined as follows: early disease included patients undergoing HCT in first remission (acute leukemia) or first chronic phase (CML) or MDS with refractory anemia or refractory anemia with ringed sideroblasts (RA, RARS); intermediate disease was defined as second or later complete remission (ALL), second or later chronic phase/accelerated phase (CML); and advanced disease included patients in relapse or primary induction failure (acute leukemia) or blast crisis (CML) or MDS with refractory anemia with excess blasts or excess blasts in transformation

†HLA-matching criteria used were as defined by Weisdorf et al.[20]: well-matched, no defined mismatches and no untested HLA locus; partially matched, only one untested or mismatched locus; and mismatched, 2 or more known or mismatched or untested HLA loci.

Development of the cGVHD risk score

Using the predictive variables identified in the preceding two paragraphs, we next developed a cGVHD risk score for overall survival or NRM. This was done in a dataset (n = 3550) in which all missing or unknown categories were deleted. Ten variables identified as significant in multivariate analysis of overall survival and NRM were used to build the cGVHD risk score. Variable-specific risk scores were constructed for each variable based on the relative risk of each category of the variable, as detailed in Table 3.

Variable-specific risk scores were summed for each patient to assign an overall risk score. Risk groups (RGs) were assigned based on the overall risk score as follows: RG1: 0-2; RG2: 3-6; RG 3: 7-8; RG 4: 9-10; RG 5: 11; and RG6: > 12. Table 4 gives the 5-year overall survival and NRM estimates for each group.

The results of risk stratification by cGVHD risk score are also given in Figure 1 (overall survival) and Figure 2 (NRM). The probability of overall survival at 5 years was 91% (95% CI:85%-97%) in RG1, followed by 67% (95% CI:65%-69%) in RG2, 51% (95% CI:46%-55%) in RG3, 40% (95% CI: 37%-43%) in RG4, 21% (95% CI: 12%-30%) in RG5, and 4% (95% CI: 0%-9%) in RG6.

The cumulative incidence of NRM at 5 years was 5% (95% CI: 1%-9%) in RG1, 20% (95% CI: 19%-23%) in RG2, 33% (95% CI: 29%-37%) in RG 3, 43% (95% CI: 40%-46%) in RG4, 63% (95% CI: 53%-74%) in RG5, and 72% (95% CI: 59%-85%) in RG6.

Table 2. Variables independently predictive of overall survival and NRM in multivariate analysis

		Overall survival		NRM	
Variable	**n**	**Relative risk (95% CI)**	***P***	**Relative risk (95% CI)**	***P***
Age, y			< .0001		< .0001
0-9	451	1.00		1.00	
10-19	666	1.35(1.11-1.37)	.0026	1.41(1.09-1.82)	.0080
20-29	905	1.31(1.08-1.58)	.0057	1.46(1.14-1.86)	.0030
30-39	1207	1.41(1.17-1.69)	.0003	1.66(1.31-2.11)	< .0001
40-49	1212	1.53(1.27-1.84)	< .0001	1.90(1.50-2.41)	< .0001
50-59	742	1.73(1.43-2.10)	< .0001	2.17(1.69-2.79)	< .0001
> 60	160	2.18(1.66-2.85)	< .0001	2.75(1.96-3.87)	< .0001
Acute GVHD			< .0001		< .0001
None	1483	1.00		1.00	
Grade I-II	2259	1.23(1.10-1.37)	.0003	1.31(1.14-1.51)	.0001
Grade III-IV	1651	1.55(1.38-1.74)	< .0001	1.71(1.48-1.97)	< .0001
Time from transplantation to cGVHD					
< 5 mo	3026	1.00		1.00	
> 5 mo	2317	0.79(0.72-0.86)	< .0001	0.84(0.75-0.94)	.0016
Serum bilirubin at cGVHD, mg/dL			< .0001		< .0001
1	2927	1.00		1.00	
1-2	982	1.11(1.00-1.24)	.0557	1.22(1.07-1.32)	.0035
> 2	926	1.65(1.48-1.84)	< .0001	1.88(1.65-2.15)	< .0001
Missing	508	1.05(0.90-1.23)	.5486	1.09(0.90-1.32)	.3747
KPS at cGVHD onset			< .0001		< .0001
< 80	1570	1.00		1.00	
80-100	3008	0.57(0.52-0.63)	< .0001	0.47(0.42-0.53)	< .0001
Unknown	765	0.67(0.59-0.76)	< .0001	0.60(0.52-0.71)	< .0001
Platelet count at cGVHD onset			< .0001		< .0001
$< 100 \times 10^9$/L	1920	1.00		1.00	
$> 100 \times 10^9$/L	2651	0.64(0.58-0.71)	< .0001	0.53(0.47-0.59)	< .0001
Unknown	772	0.81(0.70-0.92)	.0014	0.76(0.65-0.89)	.0006
HLA group			< .0001		< .0001
HLA sibling	1967	1.00		1.00	
Other related	226	1.38(1.13-1.70)	.0019	1.37(1.07-1.77)	.0137
Well-matched unrelated	1261	1.03(0.91-1.17)	.6405	1.00(0.86-1.16)	.9863
Partially matched unrelated	1060	1.11(0.98-1.26)	.0931	1.17(1.01-1.36)	.0360
Mismatched unrelated	532	1.37(1.18-1.59)	< .0001	1.51(1.26-1.80)	< .0001
Missing HLA data	297	0.93(0.75-1.15)	.4831	1.02(0.79-1.30)	.8950
Disease status at BMT					< .0001
Early	2957	1.00		1.00	
Intermediate	1366	1.22(1.10-1.36)	.0001	0.99(0.88-1.13)	.0137
Advanced	1020	1.86(1.68-2.05)	< .0001	1.83(1.22-1.57)	< .0001
GVHD prophylaxis					< .0001
T-cell depletion	1243	1.00		1.00	
CSA ± MTX ± other	3340	0.81(0.73-0.90)	< .0001	0.77(0.68-0.87)	< .0001
FK506 ± MTX ± other	760	1.12(0.98-1.28)	.1108	1.07(0.91-1.27)	.4099
Sex match			< .0001		< .0001
Male donor → male recipient	1805	1.00		1.00	
Male donor → female recipient	1104	0.91(0.81-1.02)	.1096	0.89(0.77-1.03)	.1087
Female donor → male recipient	1378	1.94(1.08-1.33)	.0009	1.25(1.10-1.42)	.0006
Female donor → female recipient	1056	1.10(0.98-1.23)	.1203	1.15(1.01-1.32)	.0428

CSA indicates cyclosporine; MTX, methotrexate; FK506:tacrolimus; and BMT, bone marrow transplantation.

Discussion

In this analysis of the largest cohort of cGVHD patients to date, we evaluated patient- and HCT-related factors, as well as objective, cGVHD-specific variables to develop a cGVHD risk score. We identified 6 different RGs based on the sum of risk factors that demonstrated a difference in overall survival and NRM.

Prior studies have identified several variables pertaining to organ involvement at the onset of cGVHD as being significant for higher mortality. For example, in a study evaluating a clinical grading system for cGVHD,[4] extensive skin involvement, thrombocytopenia, and progressive onset of cGVHD were identified to be significant predictors of disease-free survival. In the present study, disease-free survival in the 4 RGs was 82%, 68%, 34%, and 3% at 10 years. The performance of this prognostic score was tested in 1105 patients from 4 cohorts.[3] The extent of skin involvement was quantified in 3 cohorts using available data. In this dataset, the mortality hazard associated with extensive skin involvement was lower in each of these test samples compared with the learning sample.

In a study by Lee et al,[7] KPS, mouth and skin involvement, diarrhea, and weight loss were found to be important, with high KPS and mouth involvement being favorable prognostic signs, and

Table 3. Assigned variable-specific risk scores for each category of the variables selected based on relative risk

Variable	Risk score
Recipient age at transplantation	
< 29 y	0
30-59 y	1
> 60 y	2
Prior acute GVHD	
None	0
Present	1
Time from transplantation to cGVHD	
> 5 mo	0
< 5mo	1
Serum bilirubin at cGVHD onset	
< 2 mg/dL	0
> 2 mg/dL	2
KPS at cGVHD onset	
> 80	0
< 80	1
Platelet count at cGVHD onset	
$< 100 \times 10^9$/L	0
$> 100 \times 10^9$/L	1
Type of donor	
HLA-identical sibling/well-matched or partially matched URD	0
Other related/mismatched URD	1
Disease status at transplantation	
Early	0
Intermediate	1
Advanced	2
Sex mismatch (donor/recipient)	
Male/ male, male/female, female/female	0
Female/male	1
GVHD prophylaxis	
CSA + MTX + other	0
Tacrolimus + MTX + other or T-cell depletion	1

CSA indicates cyclosporine; and MTX, methotrexate.

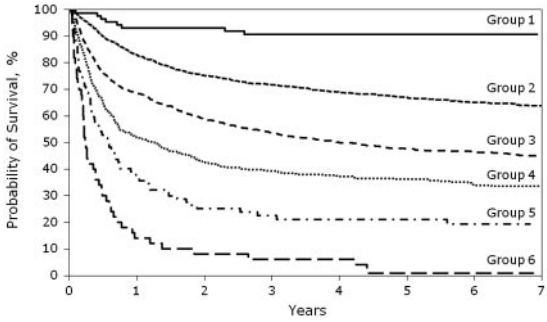

Figure 1. Overall survival by cGVHD risk score. Shown is the probability of overall survival by cGVHD risk score. $P < .01$ for all comparisons of overall survival (RG1 vs RG2 vs RG3 vs RG4 vs RG5 vs RG6).

skin involvement, diarrhea, and weight loss being unfavorable factors. Lee et al also evaluated 2 other grading schemes (limited/extensive and mild/moderate/severe) for predicting survival. Three prognostic groups were devised in which survival was statistically different in a training dataset. Low-risk patients had a high KPS (> 80%) and no diarrhea or weight loss. High-risk patients had high KPS, diarrhea, and weight loss or low KPS with either no oral involvement or all 3 poor prognostic signs: diarrhea, weight loss, and skin involvement. This was validated in 2 separate datasets. In the first validation dataset, low-risk patients had better survival than the intermediate- and high-risk groups and the intermediate- and high-risk groups were similar. In the NMDP validation set, patients with low-, intermediate-, and high-risk cGVHD had statistically different survival times. Our analysis similarly found KPS and platelet count at onset of cGVHD to be significant for survival. However, we incorporated other HCT and patient characteristics that are readily available at the time of cGVHD diagnosis into our model while developing the cGVHD risk score.

In a study by Stewart et al,[11] 751 patients with cGVHD were evaluated to determine factors associated with discontinuation of immunosuppression and NRM. Similar to our study, NRM was increased in patients with HLA mismatch, hyperbilirubinemia, increased age, thrombocytopenia at cGVHD onset, and progressive onset of disease. Stewart et al also reported increased NRM among recipients with older donors and those receiving a higher dose of prednisone immediately before the onset of cGVHD.

In a more recent analysis[19] evaluating prognostic criteria for NRM in a cGVHD cohort as defined by NIH consensus criteria, the same 6 variables reported in their prior analysis (as given in the preceding paragraph) were found to be significant except donor age at transplantation. However, both of these studies included recipients of myeloablative transplantations with bone marrow as the source of stem cells in approximately 80% of recipients.

With recent changes in transplantation strategies, there is increasing use of alternative donor sources including umbilical cord blood, more frequent use of peripheral blood stem cells and reduced intensity or nonmyeloablative conditioning, and older recipient age at transplantation. Therefore, our study included a large, multicenter cohort of all donor sources, all graft sources, and all ages. We included patients who had undergone a nonmyeloablative or reduced intensity transplantation, but this constituted only 11% of our cohort. Similar to the recent analysis, we did not find an impact of graft source on NRM or overall survival. In the study by Stewart et al,[11] the use of peripheral blood stem cells was associated with the need for prolonged immunosuppression but this

Table 4. Five-year overall survival and NRM by cGVHD risk score*

Risk group	Overall risk score	n	Overall survival (95% CI)†	NRM (95% CI)‡
RG1	0-2	90	90.8 (84.6-96.9)	4.6 (0,2-9.1)
RG2	3-6	1712	67.1 (69.4-69.4)	20.4 (18.5-22.6)
RG3	7-8	627	50.5 (46.4-54.6)	33.2 (29.1-36.8)
RG4	9-10	984	40.2 (37.0-43.3)	43.2 (40.1-46.4)
RG5	11	87	21.0 (12.2-29.8)	63.4 (53.3-73.6)
RG6	> 12	50	4 (0-9.4)	72.0 (59.4-84.6)
RG5 and RG6	> 11	137	14.5 (8.5-20.6)	66.9 (58.9-74.9)

*Shown is the probability of overall survival (95% CI) at 5 years and the cumulative incidence of NRM (95% CI) at 5 years.

†$P < .01$ for all comparisons of overall survival (RG1 vs RG2 vs RG3 vs RG4 vs RG5 vs RG6 and RG4 vs RG5 + 6).

‡$P < .01$ for the following comparisons of NRM: RG1 vs RG2 vs RG3 vs RG4 vs RG5. RG5 vs RG6 was not significant ($P = 0.2984$). For RG4 vs RG5 and RG6, $P < .0001$.

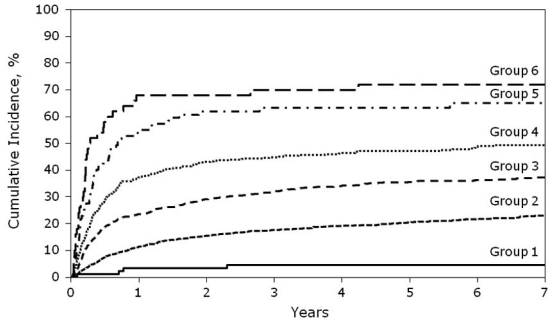

Figure 2. NRM by cGVHD risk score. Shown is the cumulative incidence of NRM by cGVHD risk score. $P < .01$ for the following comparisons for NRM: RG1 vs RG2 vs RG3 vs RG4 vs RG5 (*P* for RG5 vs RG6 was not significant at .2984).

did not affect NRM. This was postulated to be related to higher CD4 T-cell counts and improved immunofunction among peripheral blood stem cell recipients compared with bone marrow recipients with chronic GVHD.[11]

With recent improvements in supportive care, a lower NRM in the coming years is anticipated. However, we did not find an impact of the year of transplantation on NRM or overall survival. This may be related to changing patient populations over the years, with more older patients undergoing transplantation, which could account for the higher mortality.[11,19]

Our patient population is selected from a time period when NIH consensus criteria were not applicable and therefore we could not test the impact of NIH staging and classification on survival and NRM. Nevertheless, the variables identified in this scoring schema can be easily obtained and applied in patients at the time of cGVHD presentation. In cGVHD trials specifically, this system could be used as a complement to the new NIH staging criteria for the purposes of obtaining better patient population descriptions and concurrent validation relative to survival and NRM.

We also recognize that persistent acute GVHD may have many features similar to progressive onset cGVHD, so we repeated the analysis after excluding patients with early progressive onset cGVHD (< 130 days from HCT). The risk score remained similarly applicable for both overall survival and NRM in this population.

The present study used the largest available multicenter cohort of cGVHD patients to develop a cGVHD risk score using patient characteristics that are easily available at the time of cGVHD diagnosis. The score demonstrates high significance in predicting both overall survival and NRM. Our scoring system, if validated, will provide a practical tool to help identify high-risk patients for further therapy and enrollment in clinical trials of HCT.

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Authorship

Contribution: M.A., J.P.K., D.J.W., D.A.J., M.E.D.F., S.S., M.M.H., and S.Z.P designed research; M.A. and A.H. collected data; M.A., J.P.K., and A.H. performed statistical analysis; M.A., J.P.K., D.J.W., A.H., D.A.J., M.E.D.F., S.S., M.M.H., and S.Z.P. interpreted data; M.A. drafted the manuscript; and C.S.C, A.U.I., J.H.A., M.B., J.-Y.C., M.S.C., L.I., M.J., T.R.K., S.J.L., E.W.P., R.P.G., A.C.S., and J.R.W. critically reviewed and revised the manuscript.

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