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Age Adjusted Hematopoietic Stem Cell Transplant Comorbidity Index Predicts Survival in a T-Cell Depleted Cohort

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Age adjusted hematopoietic stem cell transplant comorbidity index predicts survival in a T-cell depleted cohort ☆

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Abstract
Objectives: Allogeneic hematopoietic stem cell transplant (HCT) continues to evolve with the treatment in higher risk patient population. This practice mandates stringent update and validation of risk stratification prior to undergoing such a complex and potentially fatal procedure. We examined the adoption of the new comorbidity index (HCT-CI/Age) proposed by the Seattle group after the addition of age variable and compared it to the pre-transplant assessment of mortality (PAM) that already incorporates age as part of its evaluation criteria.
Methods: A retrospective analysis of adult patients who underwent HCT at our institution from January 2010 through August 2014 was performed. Kaplan-Meier's curve, log-rank tests, Cox model and Pearson correlation was used in the analysis.
Results: Of the 114 patients that underwent allogeneic transplant in our institution, 75.4% were $\geq$40 years old. More than 58% had a DLCO $\leq$80%. Although scores were positively correlated (correlation coefficient 0.43, $p < 0.001$), HCT-CI/Age more accurately predicted 2-year overall survival (OS) and non-relapse mortality (NRM) in patients with lower (0—4) and higher

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(5—7) scores (52% and 36% versus 24% and 76%, $p = 0.004$, 0.003 respectively). PAM score did not reach statistical significance for difference in OS nor NRM between the low (<24) and high-risk (≥24) groups ($p = 0.19$ for both).

Conclusions: Despite our small sample population, HCT-CI/Age was more discriminative to identify patients with poor outcome that might benefit from intensified management strategies or other therapeutic approaches rather than allogeneic HCT.

Introduction

Allogeneic hematopoietic cell transplantation often presents the only curable therapeutic option for patients suffering from hematologic malignancies. While originally available to the young and fit, it is being increasingly utilized for patients of older age and with more comorbidities [1]. An inverse correlation of conditioning related toxicity and a better understanding of the graft versus leukemia effect, have led to allogeneic HCT being available for those patients in their 6th and 7th decade of life [2—4].

However, it is crucial to understand treatment related mortality from HCT in order to better identify those patients who would benefit from an alternative treatment approach or intensified supportive measures to optimize their outcome.

The first attempts to predict outcome were made using the Charlson comorbidity index (CCI) [5] in 2004 when its application in 134 allogeneic HCT recipients allowed to predict non-relapse mortality in myeloablative and non-myeloablative regimens [6]. The same group used a larger cohort to create the Hematopoietic stem cell transplant comorbidity index (HCT-CI), which added variables such as obesity, psychiatric disturbances and infection to the pre-transplant evaluation [7]. Since then, this scoring system has been accepted in multiple institutions as a commonly used tool for evaluating patients undergoing allogeneic HCT including our transplant center.

In an attempt to include more variables such as age, disease status and source of graft as potential factors on transplant outcome, Pariman et al formed a 50 points scoring system, the pre-transplant assessment of mortality (PAM) score. Both scoring systems have been validated in different patient populations [8—11]. Age has been a controversial predictor in transplant outcome; a study from the US showed poor prediction of allogeneic HCT mortality when elderly patients were stratified by age [12]. The European experience reported similar outcome of patients with age above 50 [13]. Sorror et al studied the effect of addition of age to HCT-CI and was able to show that age ≥40 years carried worse prognosis and deserved to be amended to HCT-CI scoring system to facilitate patients' stratification prior to transplant [14].

Since this introduction of age variable to HCT-CI score, to our knowledge, there have been no studies to verify the utility of this new scoring system and how it compares to the PAM score in an independent patient cohort. We aimed to compare the two scores and to verify their applicability in our population.

Methods

This is a retrospective analysis of 114 consecutive patients who underwent allogeneic HCT at the University of Kentucky between January 2010 and August 2014. The study was approved by the institutional review board.

Patients and transplant procedure

All adults, 18 years or older, carrying a diagnosis of malignant or benign conditions warranting an allogeneic HCT were included. Data including pre-transplant organ function, underlying disease, and donor type (matched sibling donor (MR), matched unrelated donor (MUD), and mismatch donor (MMR)) [15]. A match was defined as 10 out of 10 HLA match. Conditioning regimens were categorized according to previously defined criteria [16]: Disease was categorized based on the revised disease risk index [17]. Myeloablative regimen (MA) included total body irradiation (TBI) of ≥5 Gy single dose or ≥8 Gy fractionation, Busulfan (Bu) >8 mg/kg orally or >4000 AUC intravenously. Non myeloablative (NMA) regimens included TBI ≤2 Gy ± a purine analog. All other regimens were considered reduced intensity regimens (RIC) including regimens containing Bu that do not meet MA definition, and Fludarabine (Flu)+Melphalan (Mel). Graft versus host disease (GVHD) prophylaxis was done with tacrolimus ± methotrexate. In vivo T cell depletion was done with alemtuzumab or ATG as part of conditioning regimen based on treating physician discretion.

Patients were kept in the hospital until neutrophil engraftment, defined as an absolute neutrophil count >50 $0 \times 10^3/\mu L$ for three consecutive days. Acute GvHD was evaluated based on predefined criteria [18]. PAM score and HCT-CI/Age were calculated for all patients as described [14,15].

Statistical analysis and end points

Using the Contal and O'Quigley method [19], the ideal cut-off points were determined for both PAM (≥24) and HCT-CI/Age (≥5) that would be able to separate the population into two groups depending on outcome. The cohort was then divided into two groups (low and high risk) using the predefined cutoff points for both comorbidity scores. Overall survival (OS) and non-relapse mortality (NRM) rates at two years were calculated and compared for both groups using Kaplan-Meier curves and log rank tests and competing risk methods respectively. Cox models were utilized to calculate

hazard ratios for OS and NRM for both risk groups using PAM and HCT-CI/Age using univariate and multivariate analysis. Pearson correlation was used to study association between PAM and HCT-CI/Age score. Multivariate analysis was explored to study whether the comorbidity score has independent effect on overall survival at 2 years. Analyses were run using SAS 9.4 (SAS Institute, Cary NC) and statistical significance was defined as p value of <0.05 for all tests.

Results

Baseline characteristics

Median age of the 114 patients included was 53 (range 20—69). Most transplanted patients were ≥40 year-old (75%, n = 86). There was similar gender distribution. Grafts from MUD represented 65% (n = 74), while only 2.6% (n = 3) were MMR. 2.6% (n = 3) had low-risk disease prior to transplant, and 8.7% (n = 10) had high-risk disease. The specific underlying disease and baseline characteristics are shown in (Tables 1 and 2).

Pre-transplant diffusion lung capacity (DLCO) of most patients (58.5%, n = 62) was ≤80%, with a median of 77% (range 52—142%). GvHD prophylaxis was done with tacrolimus (100%, n = 114), and methotrexate (83%, n = 94), and in-vivo T cell depletion was incorporated in the GvHD prophylaxis in 80% (n = 91). Similar number of patients received T cell depletion with alemtuzumab (38%, n = 43) versus ATG (42%, n = 48). Reduced intensity conditioning was used in 49% (n = 50), while only 1.7% (n = 2) patients received non-myeloablative conditioning regimen. Details of the conditioning regimens used are shown in Table 3.

Outcome for patients using stratification by HCT-CI/Age score

Using HCT-CI/Age score, 92 patients (80.7%) were grouped into a low-risk (0—4), 21 (18.4%) into high-risk (5—7) category with 1 (0.9%) not evaluable. OS at 2 years for the low-risk group was 52.4% (95% Confidence interval (CI):

Table 1 Baseline characteristics of the full cohort.

Variables		N	%
Age	<40	28	24.6
	≥40	86	75.4
Gender	Male	60	52.6
	Female	54	47.4
CMV patient	Positive	70	61.4
	Negative	27	23.7
	Unknown	17	14.9
CMV donor	Positive	50	43.9
	Negative	46	40.4
	Unknown	18	15.8
Donor	MR	37	32.5
	MUD	74	64.9
	MMR	3	2.6
Pre-transplant creatinine	≤1.2 (mg/dL)	105	92.1
	>1.2 (mg/dL)	9	7.9
Pretranplant alanine transferase	≤49 (U/L)	88	77.9
	>49 (U/L)	25	22.1
Pretransplant FEV1	>80%	82	78.1
	≤80%	23	21.9
Pretransplant DLCO	>80%	44	41.5
	≤80%	62	58.5
Underlying disease	AML	49	43.0
	ALL	19	16.7
	MDS	19	16.7
	CML	4	3.5
	CLL	5	4.4
	MF	5	4.4
	HL	4	3.5
	NHL	3	2.6
	AA	2	1.8
	Others (T-PLL, MPN, HLH)	4	3.5

Table 2 Comparison of baseline characteristics between the different groups of the pretransplant scores.

Variables		HCT-CI/Age			PAM		
		Low (%)	High (%)	*P*	Low (%)	High (%)	*P*
Age	<40	96	4	0.01	56	44	0.24
	≥40	77	23		66	34	
Gender	Male	80	20	0.39	54	46	0.03
	Female	83	17		73	27	
CMV patients	Positive	81	19	0.45	67	33	0.32
	Negative	78	22		59	41	
CMV donor	Positive	80	20	0.60	72	28	0.07
	Negative	80	20		56	44	
Donor type	MR	81	19	0.70	81	19	0.01
	MUD	81	19		54	46	
	MMR	100	0		67	33	
Disease risk index	Low	82	18	0.99	76	24	0.32
	Intermediate	81	19		58	42	
	High	82	18		64	36	
Conditioning regimen	NMA	100	0	0.59	100	0	0.36
	RIC	78	22		67	33	
	MA	84	16		58	42	

Table 3 Pretransplant conditioning and GvHD prophylaxis.

		N	%
Conditioning regimen	FLU/MEL	41	36.0
	BU/FLU	28	24.6
	BU/CY	26	22.8
	CY/TBI	17	14.9
	ET/TBI	2	1.8
GvHD prophylaxis	Tacrolimus	114	100
	MTX	94	82.5
In-vivo T cell depletion	ATG	48	42.1
	Alemtuzumab	43	37.7

40.5—63%) versus 23.8% (95% CI: 8.7—43%) for the high-risk group ($p = 0.004$) (Fig. 1).

NRM mortality at two years was 36.2% (95% CI: 24.6—47.8%) versus 75.6% (95% CI: 45.4—90.5%) for the low and high-risk group respectively ($P = 0.004$) (Fig. 2).

Using univariate analysis, the hazard ratio (HR) for death in the high-risk group was 2.26 (95% CI: 1.28—4) with a $P = 0.005$. When adjusting for other variables (gender, CMV status, graft source, acute GvHD grade, and chronic GvHD severity), HCT-CI/Age risk stratification was the only statistically significant variable to affect survival with a HR of 2.16 (95% CI: 1.11—4.18).

Outcome for patients using stratification by PAM score

The calculated threshold for the PAM score to best separate patients by outcome was 24, and 47 patients (41.2%) were

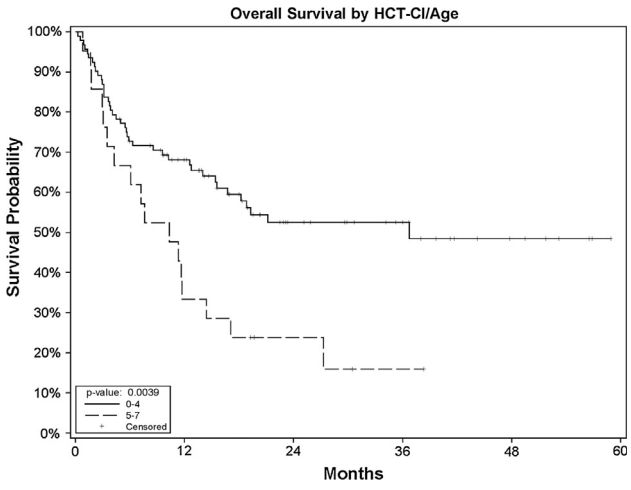

Fig. 1 OS by HCT-CI/Age.

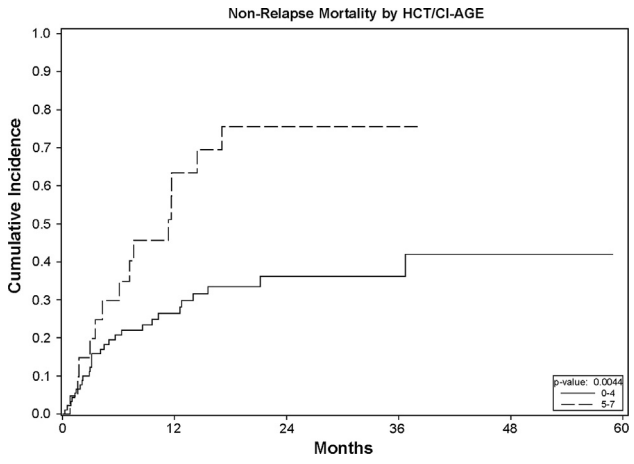

Fig. 2 NRM by HCT-CI/Age.

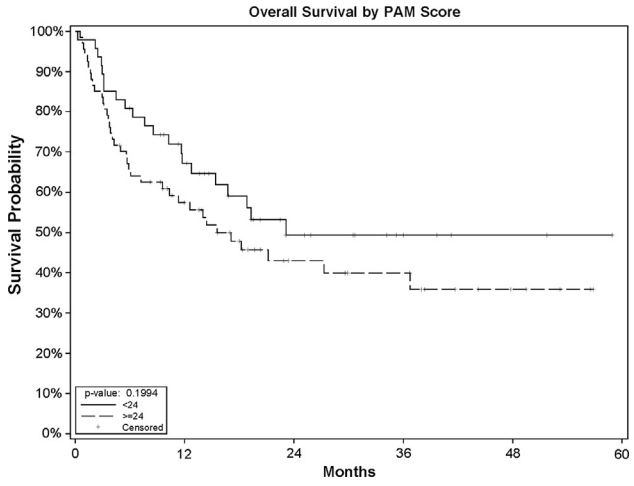

Fig. 3 OS by PAM.

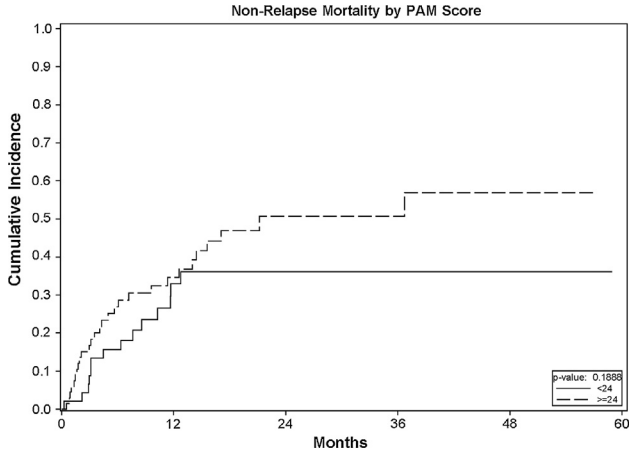

Fig. 4 NRM by PAM.

accordingly stratified into low-risk (<24) and 67 (58.8%) into high-risk (≥24). There was no difference in the low risk group for OS at 2 years when compared to the high-risk group (49.4% versus 43% respectively) ($p = 0.199$) (Fig. 3).

The 2-year NRM difference between the two groups did not reach statistical significance either (36.1 versus 50.7% respectively) ($p = 0.190$) (Fig. 4).

Using Pearson correlations, we showed a slightly positive correlation between the HCT-CI/Age and PAM score (correlation coefficient 0.427, $p < 0.001$).

Discussion

Both HCT-CI/Age and PAM have been described to predict transplant associated morbidity and mortality. Several studies have demonstrated different cutoff needs to be used for different patient cohorts in order to validate the usefulness of pretransplant scores [9,11,20,21]. Our cutoff for the HCT-CI/Age was consistent with the one reported by the Seattle group [14]; however, due to smaller patient number we elected to divide the patients into two groups rather than 4. While our population overall tended to be older and patients received mostly reduced intensity conditioning and T cell depletion when compared to the original Seattle cohort, we were still able to retrospectively validate the ability of the HCT-CI/Age to separate patients into high and low risk groups with respect to transplant outcome, hereby supporting the usefulness of the HCT-CI/Age. High-risk patients at our center had comparable survival at 2 years with high-risk groups reported in previous studies [7,13,21,22].

The fact that PAM score did not correlate with survival despite selecting an optimum cutoff point, that should have translated to best separation in risk groups, possibly relates to the smaller sample size, however, it may also relate to differences in our cohort from the original PAM score [15]. In comparison to the population used to develop PAM, we had older patients, with worse pulmonary function and most of them had received T cell depletion with RIC HCT. More recent reports support our findings, showing poor predictability of PAM in T-cell depleted population [23] and less strong association with mortality when RIC regimens were used [24].

Limitations to our study include the retrospective nature, which could have been affected by selection bias with respect to transplant eligibility of patients and choice of conditioning regimen. Our small population size and lack of variable graft sources make it impractical to translate those findings to haploidentical and cord blood transplants [21]. A strength of our study possibly relies in the homogenous selection from a consistent geographical area to support similarities in environmental and genetic factors.

In summary, our study validates and supports the use the novel HCT-CI/Age score to predict outcome and to allow for a more informed counselling process for our patients undergoing allogeneic HCT. Our results further confirm the previous reported decreased usefulness of the PAM score with the evolution of allogeneic HCT using RIC approaches offered to a higher risk patient population.

Conflict of interest

There is no conflict of interest to be reported by the authors

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