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Supportive Care

Hematopoietic Cell Transplant–Related Toxicities and Mortality in Frail Recipients



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A B S T R A C T

Frailty is a state characterized by diminished physiologic reserve and increased vulnerability to stress and adversely affects outcomes in older patients. We aimed to determine the relationship between pre-hematopoietic cell transplant (HCT) frailty and grades 3 to 4 nonhematologic toxicities (Common Terminology Criteria for Adverse Events, version 5.0) and mortality in HCT recipients within 1 year after HCT and also examined whether age at HCT moderated that association. In a prospective longitudinal study of 117 patients aged ≥ 40 years undergoing HCT, we performed formal pre-HCT geriatric assessments. Frailty was assessed using Fried's criteria. Post-HCT toxicities were abstracted through medical record reviews. The prevalence of pre-HCT frailty was 21% and was not different in younger (40 to 59 years) versus older (≥ 60 years) HCT recipients. Overall, frail recipients (versus nonfrail) had a higher cumulative incidence of any grades 3 to 4 nonhematologic toxicity (86% [95% confidence interval {CI}, 62% to 100%] versus 70% [95% CI, 57% to 83%], $P = .03$) and more organ-specific grades 3 to 4 toxicities, such as non-neutropenic infections (38% [95% CI, 17% to 59%] versus 13% [95% CI, 6% to 20%], $P < .01$), nervous system disorders (19% [95% CI, 3% to 35%] versus 4% [95% CI, 0 to 8%], $P = .02$), and pneumonia (38% [95% CI, 17% to 59%] versus 10% [95% CI, 4% to 17%], $P < .01$). Frail recipients were 1.9-fold (95% CI, 1.1 to 3.4) more likely to develop any grades 3 to 4 toxicities ($P = .03$), 4-fold more likely to suffer non-neutropenic infections (95% CI, 1.4 to 11) and pneumonia (95% CI, 1.4 to 12; both $P = .01$), and 8.6-fold (95% CI, 1.6 to 45.3) more likely to suffer nervous system disorders ($P = .01$). Frail allogeneic HCT recipients also had a 3.1 times (95% CI, .9 to 9.7; $P = .06$) higher risk of overall mortality as compared with nonfrail allogeneic HCT recipients. The higher toxicity and mortality observed in frail allogeneic recipients needs to be monitored with high attention. Studies focusing on interventions to reduce frailty and manage morbidities are needed.

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INTRODUCTION

Frailty is a state characterized by diminished physiologic reserve and increased vulnerability to stress and adversely affects outcomes in older patients [1]. The prevalence of frailty increases with age and approaches 10% in community-dwelling elderly [2]. Advances in transplant strategy and supportive care have enabled an increasing number of hematopoietic cell transplants (HCTs) to be performed in older individuals with

malignant and nonmalignant disorders. Currently, 31% of all allogeneic transplants performed annually in the United States are in those older than 60 years of age [3].

Geriatric assessments are not routinely used to screen older HCT recipients, and there is limited information regarding frailty in patients undergoing HCT. Furthermore, the impact of frailty on post-HCT nonhematologic severe or life-threatening toxicities is not known. We addressed these gaps by undertaking a prospective longitudinal study to evaluate pre-HCT frailty in patients aged ≥ 60 years and compared them with a cohort of younger (40 to 59 years) HCT recipients undergoing HCT at the University of Minnesota. We also examined the impact of pre-HCT frailty on post-HCT Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) grades 3 to 4 (severe and

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life-threatening) nonhematologic toxicities and overall mortality by 1 year after HCT.

METHODS

Study Population

Patients undergoing HCT (autologous or allogeneic) at age ≥ 40 years at the University of Minnesota between March 2014 and July 2015 were eligible for participation. Of the 140 eligible patients, 117 (83.6%) participated. The study was approved by the University of Minnesota Institutional Review Board. All participants signed an informed consent before enrollment.

Study Measures

All patients completed a questionnaire and assessment pertaining to the following domains of geriatric assessment pre-HCT: physical functioning, comorbid medical conditions, cognition, nutritional status, psychological status, social activity, and social support [4]. All assessments were performed within 2 weeks before the start of the conditioning regimen. Patients were consented during workup for HCT, and assessments were performed either in the clinic or on admission before the start of the conditioning regimen.

Definition of Frailty

The frailty phenotype was constructed using responses to the questionnaire [5,6] (Supplementary Table 1) along with clinical assessment to evaluate 5 indices. The first index was unintentional weight loss, which was a self-report of involuntary weight loss of $>5\%$ or >10 pounds in the past 6 months, scored as 1 point [7–9]. The second index was exhaustion, also a self-report of the inability to carry on normal activity or work or need for assistance, scored as 1 point. Slow walking speed, the third index, was assessed using the timed up and go test. This test measures the number of seconds it takes an individual to stand up from a standard armchair (approximate seat height of 46 cm), walk a distance of 3 m (10 ft), turn, walk back to the chair, and sit down again). A time of ≥ 20 seconds was scored as 1 point [10]. The fourth index, weakness, was assessed by a self-report of one's ability to lift and carry groceries. Inability was scored as 1 point. The fifth index was low energy expenditure, evaluated by using the physical functioning domain of the Medical Outcomes Study Short Form, 10-item questionnaire [11,12]. A score < 85 (cut-off based on recursive partitioning) [13] scored 1 point. A frailty score was computed by adding up the scores of each index. Individuals with a score ≥ 3 were considered frail; those with a score < 3 were considered nonfrail [9].

Disease Risk

The disease risk index was used to categorize disease risk as previously defined [14].

Scoring of Post-HCT Nonhematologic Toxicities

Scoring was based on the CTCAE, version 5.0, to determine the severity of the toxicity. Data were abstracted through medical record reviews and correspondence from other treating physicians. The CTCAE has been used to grade health conditions in cancer survivors [15] and distinguishes grades 1 through 5 with unique clinical descriptions of the severity for each event (grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, life-threatening/disabling; grade 5, death related to toxicity). Among allogeneic HCT recipients, patients with grades III to IV acute graft-versus-host disease or moderate and severe chronic graft-versus-host disease needing systemic immune suppression were considered to have grades 3 to 4 nonhematologic toxicity.

Study Outcomes

Study outcomes included prevalence of frailty pre-HCT in the older group (≥ 60 years) compared with the younger group (40 to 59 years) and impact of pre-HCT frailty on the incidence of post-HCT severe and life-threatening (grades 3 to 4) nonhematologic toxicities and overall mortality within 1 year post-HCT.

Statistical Analysis

Demographic and clinical characteristics were compared between the 2 groups (frail and nonfrail) by using the chi-square test and the general Wilcoxon tests. Prevalence of frailty was estimated pre-HCT among assessable patients ($n=98$). Nonassessable patients ($n=19$, not assessable due to 1 or more missing measures of frailty) were more likely to have undergone autologous HCT (74% versus 52%, $P=.05$) and less likely to have undergone HCT using reduced-intensity conditioning (11% versus 38%, $P=.02$). Overall survival was estimated using Kaplan-Meier curves, and 95% confidence intervals (CIs) were calculated using the Greenwood formula [16]. Grades 3 to 4 nonhematologic toxicity was analyzed using cumulative incidence, treating death as a competing risk [17]. Gray's test was applied for comparisons of 2 categories [18]. Fine and Gray proportional hazards regression was used to assess the independent effect of frailty on various toxicities [18]. Prespecified factors considered in the regression models were frailty, age (40 to 50 versus 51 to 60 versus ≥ 60), donor type (autologous versus allogeneic), disease risk

index, conditioning (myeloablative versus reduced intensity), and HCT-specific comorbidity index [19] (low risk [score 0] versus intermediate risk [score 1 to 2] versus high risk [score 3+]). All analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Prevalence of Frailty

Frailty was assessable in 98 patients (84%): 51 autologous and 47 allogeneic. The prevalence of frailty pre-HCT was 21%. Table 1 shows patient and transplant characteristics. The median age of frail patients was 61 years (range, 51 to 70) versus 59 years (range, 40 to 73) in nonfrail patients ($P=.25$). The prevalence of frailty did not differ by age. The prevalence was 19% in the younger age group (40 to 59 years) versus 24% in the older age group (≥ 60 years; $P=.8$). An allogeneic HCT was performed in 57% and 45% of frail and nonfrail patients ($P=.59$). The prevalence of frailty was also not different by donor type. The prevalence was 18% in autologous HCT recipients versus 26% in allogeneic HCT recipients pre-HCT ($P=.08$). Reduced-intensity conditioning was applied in 52% versus 34% of frail and nonfrail patients, respectively. Pre-HCT comorbidity index was high in 38% versus 23%, intermediate in 43% versus 39%, and low in 19% versus 38% of frail and nonfrail recipients ($P=.21$). No differences were noted in time to neutrophil engraftment, length of initial hospitalization, and number of readmissions between the frail and nonfrail recipients (all $P>.1$).

Grades 3 to 4 Nonhematologic Toxicities within 1 Year Post-HCT

Frail recipients (versus nonfrail) had a higher cumulative incidence of any nonhematologic grades 3 to 4 toxicity (86% [95% CI, 62% to 100%] versus 70% [95% CI, 57% to 83%], $P=.03$) by 1 year post-HCT (Table 2 and Figure 1A). In multiple regression analysis, adjusted for age at HCT (40 to 50 versus 51 to 60 versus >60 years), donor type (autologous versus allogeneic), conditioning intensity (myeloablative versus reduced-intensity conditioning), and HCT-specific comorbidity index, frail recipients were 1.9 times (95% CI, 1.1 to 3.4; $P=.03$) more likely to develop any grades 3 to 4 nonhematologic toxicity than nonfrail recipients (Table 3). We also evaluated the risk of any grades 3 to 4 nonhematologic toxicities separately in autologous and allogeneic HCT recipients (data not shown). Among allogeneic frail recipients (relative risk [RR], 2.4; $P=.04$) a higher risk of grades 3 to 4 nonhematologic toxicities was seen in frail recipients. Among autologous recipients this did not attain statistical significance (RR, 1.4; $P=.4$).

Organ-Specific Toxicities

The cumulative incidence of organ-specific toxicities among frail and nonfrail recipients is detailed in Table 2. Frail recipients had a higher cumulative incidence of non-neutropenic infections (38% [95% CI, 17% to 59%] versus 13% [95% CI, 6% to 20%], $P<.01$), nervous system disorders (19% [95% CI, 35% to 35%] versus 4% [95% CI, 0 to 8%], $P=.02$), and pneumonia (38% [95% CI, 17% to 59%] versus 10% [95% CI, 4% to 17%], $P<.01$) (Figure 1B–D).

In multiple regression analysis, after controlling for age at HCT (40 to 50 versus 51 to 60 versus >60 years), donor type (autologous versus allogeneic), conditioning (myeloablative versus reduced-intensity conditioning), and HCT-specific comorbidity index, frail recipients had a 4 times higher risk of developing non-neutropenic infections (RR, 4.0; 95% CI, 1.4 to 11; $P=.01$) and pneumonia (RR, 4.1; 95% CI, 1.4 to 12.0; $P=.01$)

Table 1
Demographic and Clinical Characteristics

	All Patients	Nonfrail	Frail	P
Patients	117 (100)	77 (79)	21 (21)	
Age at HCT, yr				
Median (range)	59 (40-73)	59 (40-73)	61 (51-70)	.25
Gender, male	67 (57)	42 (55)	15 (71)	.16
Diagnosis				.36
Acute leukemia	27 (23)	17 (22)	7 (33)	
Lymphoma	39 (33)	30 (39)	4 (19)	
Multiple myeloma	35 (30)	19 (25)	7 (33)	
Other	16 (14)	11 (14)	3 (14)	
Disease risk index	78 (67)	50 (65)	16 (76)	.86
Low	13 (11)	10 (13)	3 (14)	
Intermediate	90 (77)	59 (77)	15 (71)	
High/very high	13 (11)	8 (10)	3 (14)	
Nonmalignant	1 (1)	0	0	
Donor type				.59
Autologous	65 (56)	42 (55)	9 (43)	
HLA identical sibling	27 (23)	17 (22)	7 (33)	
Matched unrelated	4 (3)	2 (3)	0	
Single UCB	2 (2)	1 (1)	1 (5)	
Double UCB	19 (16)	15 (19)	4 (19)	
Conditioning, reduced intensity	39 (33)	26 (34)	11 (52)	.12
Conditioning agents				.33
Cy/TBI	12 (10)	7 (9)	3 (14)	
Cy/Flu/TBI	24 (21)	18 (23)	4 (19)	
Cy/Flu/TBI/ATG	13 (11)	8 (10)	5 (24)	
Chemotherapy only	68 (58)	44 (57)	9 (43)	
GVHD prophylaxis (allogeneic HCT)				.75
CsA/MMF	26 (50)	16 (46)	7 (58)	
CsA/MTX or CsA only	12 (23)	8 (23)	2 (17)	
Sirolimus/MMF	14 (27)	11 (31)	3 (25)	
Recipient/donor CMV serostatus				.14
-/- or auto -	48 (41)	36 (47)	6 (29)	
Other	69 (59)	41 (53)	15 (71)	
Race, nonwhite	5(4)	1 (1)	4 (19)	<.01
Comorbidity (HCT-specific comorbidity index)				.21
Low risk (0)	40 (34)	29 (38)	4 (19)	
Intermediate risk (1-2)	47 (40)	30 (39)	9 (43)	
High risk (3+)	30 (26)	18 (23)	8 (38)	
Year of transplant				.59
2014	73 (62)	54 (70)	16 (76)	
2015	44 (38)	23 (30)	5 (24)	
Median follow-up, mo (range)	24 (13-29)	26 (15-29)	23 (13-29)	.16
Autologous HCT				
ANC engraftment*				
Median days (range)	11 (2-12)	11 (2-12)	10 (9-12)	.37
Length of initial hospitalization				
Median days (range)	7 (3-29)	7 (3-29)	3 (3-9)	.23
Readmissions in first year				.16
0	25 (38)	19 (45)	2 (22)	
1	27 (42)	16 (38)	3 (33)	
2	13 (20)	7 (17)	4 (44)	
Allogeneic HCT				
ANC engraftment*				
Median days (range)	12 (0-32)	13 (0-32)	9.5 (6-32)	.45
Length of initial hospitalization				
Median days (range)	29 (15-127)	29 (15-127)	37.5 (15-69)	.29
Readmissions in first year				.40

(continued)

Table 1 (Continued)

	All Patients	Nonfrail	Frail	P
0	21 (40)	17 (49)	4 (33)	
1	12 (23)	8 (23)	2 (17)	
2	19 (37)	10 (29)	6 (38)	

Values are n (%) unless otherwise defined. UCB indicates umbilical cord blood; Cy, cyclophosphamide; TBI: total body irradiation; flu, fludarabine; ATG, antithymocyte globulin; CsA, cyclosporine; MTX, methotrexate; MMF, mycophenolate; GVHD, graft-versus-host disease; CMV, cytomegalovirus; ANC, absolute neutrophil count.

* ANC engraftment was defined as the first of 3 consecutive days of neutrophil counts of $.5 \times 10^9$ or higher.

Table 2

Cumulative Incidence (95% CI) of Grades 3 to 4 Nonhematologic Toxicities by 1 Year Post-HCT

Toxicity	Nonfrail (n = 77)	Frail (n = 21)	P
Neutropenic fever	58 (46-71)	67 (44-90)	.12
	7 (1-141)	5 (0-9)	
Cardiac	3 (0-6)	5 (0-14)	.58
	98 (85-110)	58	
Ear and labyrinth disorders	1 (0-4)	0	NA
	11		
Endocrine disorders	0	0	NA
Eye disorders	0	0	NA
Gastrointestinal disorders	22 (13-31)	19 (3-35)	.71
	8 (4-151)	43 (8-93)	
Hepatobiliary disorders	0	0	NA
Non-neutropenic infections	13 (6-20)	38 (17-59)	<.01
	43 (14-315)	36 (16-223)	
Fall	0	0	NA
Fracture	0	0	NA
Metabolism and nutrition disorders	31 (21-42)	52 (30-75)	.08
	8 (2-89)	9 (1-78)	
Musculoskeletal and connective tissue disorders	0	5 (0-14)	NA
		81	
Neoplasms benign, malignant (secondary)	3 (0-6)	0	NA
	197 (196-198)		
Nervous system disorders*	4 (0-8)	19 (3-35)	.02
	13 (3-94)	29 (7-211)	
Psychiatric disorders	0	0	NA
Renal and urinary disorders	6 (1-12)	10 (0-22)	.66
	12 (10-85)	41 (26-55)	
Reproductive and breast disorders	0	0	NA
Respiratory, thoracic, and mediastinal disorders	18 (10-27)	24 (6-42)	.58
	16 (5-109)	17 (6-79)	
Pneumonia	10 (4-17)	38 (17-59)	<.01
	23 (1-317)	39 (6-103)	
Social circumstances	0	0	NA
Vascular disorders	1 (0-4)	5 (0-14)	.30
	58	242	
Surgical and medical procedures	2 (0-6)	0	NA
	170		
Grades III to IV acute GVHD (allogeneic only)	6 (0-13)	8 (0-23)	.78
	42 (28-55)	35	
Chronic GVHD (allogeneic only)	11 (1-22)	0	.30
	204 (161-233)		
Any grades 3-4 toxicity	70 (57-83)	86 (62-100)	.03
	7 (1-315)	6 (0-61)	
1-Year mortality	19 (11-28)	52 (30-75)	<.01

Per each row, top values are cumulative incidence in percents (95% CI) and bottom values are median days (range) to first onset. NA indicates not assessable.

* These included stroke (n = 1), encephalopathy (n = 2), and severe dizziness and neuropathy (n = 1) in frail patients and encephalopathy (n = 1) and severe neuropathy (n = 2) in nonfrail patients. Bold values are statistically significant with a p-value of <0.05.

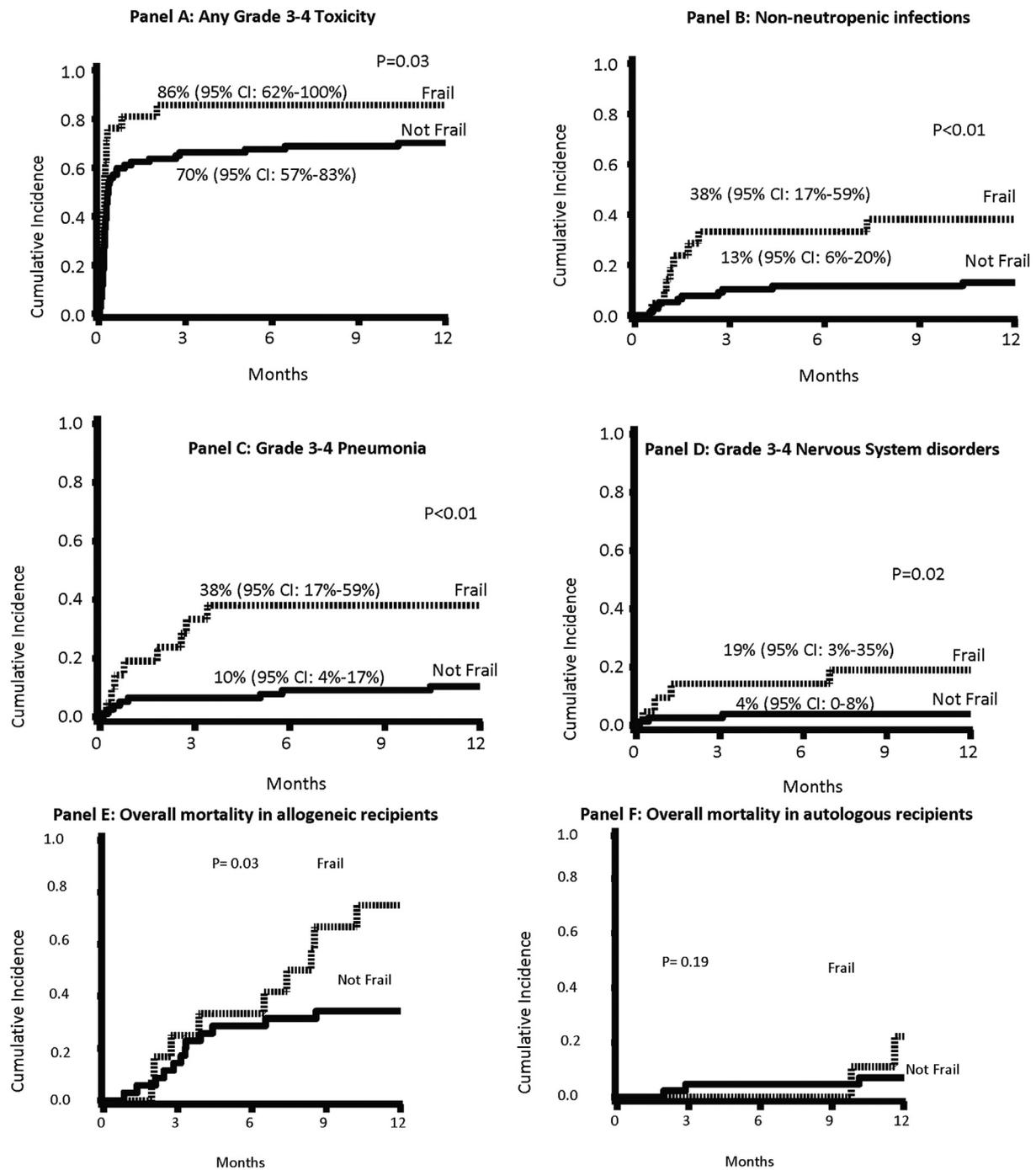


Figure 1. Cumulative incidence of (A) any grades 3 to 4 nonhematologic toxicities, (B) non-neutropenic infections, (C) grades 3 to 4 pneumonia, (D) grades 3 to 4 nervous system disorder, (E) overall mortality by 1 year in allogeneic recipients, and (F) overall mortality by 1 year in autologous recipients.

and an 8.6-fold higher risk of developing nervous system disorders (RR, 8.6; 95% CI, 1.6 to 45.3; $P = .01$) (Table 3).

Overall Mortality

The incidence of overall mortality by 1 year post-HCT was 52% (95% CI, 30% to 75%) in frail recipients versus 19% (95% CI, 11% to 28%) in nonfrail recipients ($P < .01$). Because of a higher overall mortality in allogeneic HCT recipients, this analysis was performed separately in autologous and allogeneic recipients (Figure 1E,F and Table 4). Among allogeneic HCT recipients, frail recipients had a 3.1-fold higher risk of overall

mortality as compared with nonfrail recipients (RR, 3.1; 95% CI, .9 to 9.7; $P = .06$). Among allogeneic HCT recipients, 21 patients died within 1 year of HCT. Causes of death were graft failure (2 frail, 1 nonfrail), graft-versus-host disease (1 frail and 2 nonfrail), infection and organ failure (1 frail and 2 nonfrail), new malignancy (1 nonfrail), and relapsed disease (5 frail and 6 nonfrail).

DISCUSSION

Our study identified 21% of recipients as frail before HCT with no differences by age, suggesting that younger patients

Table 3

Multivariate Analysis: Specific Grades 3 to 4 Toxicities within 1 Year of HCT

Variable	No. of Cases	Any Grades 3–4 Toxicity		Non-Neutropenic Infections		Pneumonia		Nervous System Disorders	
		RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Frailty									
Nonfrail	77	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
Frail	21	1.9 (1.1–3.4)	.03	4.0 (1.4–11.0)	.01	4.1 (1.4–12.0)	.01	8.6 (1.6–45.3)	.01
Age, yr									
40–50	10	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	NA
51–60	43	1.2 (.5–2.9)	.74	1.6 (.2–12.0)	.64	1.2 (.1–10.7)	.89	NA	
>60	45	1.4 (.5–3.7)	.47	1.3 (.2–8.4)	.78	.9 (.1–7.2)	.90	NA	
Donor type									
Autologous	51	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
Allogenic	47	3.3 (1.6–6.8)	<.01	6.9 (1.5–32.8)	.01	4.8 (.7–31.0)	.10	1.0 (.1–28.8)	.98
Conditioning									
MA	61	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
Reduced intensity	37	.3 (.2–.6)	<.01	.2 (.1–.7)	.01	.6 (.1–2.9)	.49	.4 (.03–4.3)	.86
HCT-specific comorbidity index									
Low risk	33	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
Intermediate	39	1.3 (.8–2.3)	.56	2.7 (.8–9.2)	.24	1.0 (.2–4.4)	.53	.7 (.1–4.0)	.83
High	26	1.1 (.6–2.1)		2.6 (.7–9.7)		1.7 (.5–6.1)		.5 (.1–5.1)	

MA indicates myeloablative.

who have suffered significant stressors of malignancy and its treatments are also at risk of developing frailty. In a prior analysis reported by Muffly et al. [20], among HCT recipients 50 years and older, a similar prevalence of frailty was noted (25%) pre-HCT and did not differ among those that were younger (50 to 59 years: 27%) versus older (60 to 73 years: 20%). Our study analyzed severe and life-threatening toxicities and overall mortality through 1 year after HCT. We observed a 1.9 times higher risk of any severe/life-threatening nonhematologic toxicity as compared with nonfrail recipients. Frail recipients were also at a 4-fold higher risk of non-neutropenic infections and pneumonia than nonfrail recipients. The biologic basis of this is poorly understood. The underlying pathophysiology of frailty includes chronic inflammation, and the phenotype includes malnutrition and lack of activity, which may increase susceptibility to infections [21]. Also, frailty has been suggested to be a marker of immune function decline in older adults and has been associated with a deficient immune response to influenza and pneumococcal immunizations that places them at high risk for these infections and their complications [22,23].

Our study also identified an 8-fold higher risk of severe or life-threatening nervous system complications in frail recipients. Reports have suggested an association of frailty with neurologic complications, particularly cognitive decline and dementia [24]. Factors such as chronic inflammation that underlie frailty may also underlie other neurologic diseases [21,24].

We also identified a 3.1-fold higher risk of mortality in frail allogeneic versus nonfrail allogeneic recipients. We evaluated causes of mortality and did not identify specific differences in causes of death between these 2 groups. In a different cohort, a prior report from the Bone Marrow Transplant Survivor

Study also found a higher risk of mortality among frail survivors of HCT [25]. We did not evaluate cause-specific mortality (nonrelapse and relapse-related mortality) because of the

Table 4

Multivariate Analysis: Overall Mortality

	RR (95% CI)	P
Autologous HCT		
Frailty		
Nonfrail	1.0	
Frail	2.2 (.3–16.4)	.43
HCT-specific comorbidity index		
0	1.0	
1–2	.8 (.1–6.3)	NS
3+	.9 (.1–11.1)	NS
Karnofsky performance status score		
90–100	1.0	
<90	2.3 (.3–17.8)	NS
Allogeneic HCT		
Frailty		
Nonfrail	1.0	
Frail	3.1 (.9–9.7)	.06
HCT-specific comorbidity index		
0	1.0	
1–2	1.4 (.5–4.1)	NS
3+	1.0 (.3–3.2)	NS
Karnofsky performance status score		
90–100	1.0	
<90	.7 (.2–2.3)	NS

NS indicates not significant.

smaller numbers in the 2 subsets (autologous and allogeneic HCT).

There are several limitations to our study. Our cohort was heterogeneous and included both autologous and allogeneic HCT recipients. In addition, there are differences between our construct of the frailty score and that proposed by Fried et al. [9]. These differences are highlighted in Supplementary Table 1. Although we carefully followed the phenotypic definition laid out by Fried et al. [9], some of our selected indices were based on self-report. We did not have an objective measure of grip strength in our assessment because some data were collected by self-report and we did not directly test grip strength. These limitations may have only captured a more advanced frail phenotype. Therefore, it is possible that the prevalence of these components of frailty are underestimated using our approach.

Our data demonstrate a higher prevalence of frailty in HCT recipients as compared with community-dwelling older persons [2]. The higher prevalence was seen in both young and old recipients, suggesting all ages undergoing HCT may be vulnerable and need direct evaluation. The higher rates of morbidity and mortality suggest a need to monitor these patients closely and plan protective interventions. Additional studies evaluating the underlying pathophysiology in these patients will also help identify mechanisms of frailty. A larger prospective study incorporating geriatric assessments and frailty measures along with biomarkers is under development through the Bone Marrow Transplant Clinical Trials Network CHARM study.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.bbmt.2019.07.030](https://doi.org/10.1016/j.bbmt.2019.07.030).

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