

Determinants of Functional Status in Long-Term Survivors of Allogeneic Hematopoietic Stem Cell Transplantation with Chronic Graft-Versus-Host Disease (GVHD)

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Chronic Graft-Versus-Host Disease (GVHD)

- Chronic GVHD affects 33%-80% of individuals who survive more than 100 days after allogeneic stem cell transplant
- Disease of immune dysregulation
- Immunosuppressive agent(s), together with good supportive management, are the mainstays of treatment
- Course is variable:
 - May persist, requiring immunosuppression for up to 20+ years following transplantation
 - In some instances cGVHD appears to dissipate gradually and immunosuppression can be tapered to discontinuation
- Lower relapse rate, presumably because of a graft-versus-tumor effect
- cGVHD is a leading cause of non-relapse mortality and serious morbidity



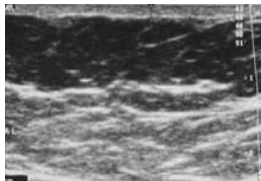
Ocular sicca



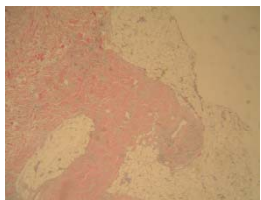
Oral ulcers



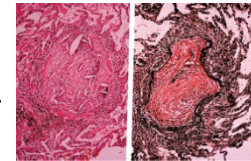
Nail dystrophy



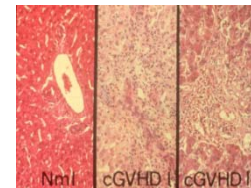
Skin sclerosis



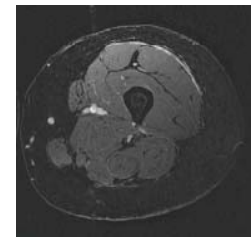
Deep sclerosis



Bronchiolitis obliterans



Loss of bile ducts



Fasciitis



Skin ulcers

Functional and Symptomatic Co-Morbidities of Chronic GVHD

- Infections
- Pulmonary impairment
- Endocrinopathies
- Arthralgias/myalgias/fasciitis/contractures
- Oral/dental complications
- Nutritional compromise
- Side effects of chronic immunosuppression
- Functional disability
- Distressing symptoms
- Body image changes
- Psychosocial distress
- Adjustment difficulties associated with chronicity

Symptoms and Functional Status in Chronic GVHD- State of the Knowledge

- No prior studies have characterized the symptom experience and functional consequences in a cohort comprised *exclusively* of allogeneic HSCT survivors experiencing chronic GVHD
- General studies of late effects following allogeneic stem cell transplantation suggest chronic GVHD may have deleterious effects on:
 - *Symptoms*
 - *Function*
 - *Quality of Life*

Strengthening the Evidence Base for Survivorship Care



Measuring Therapeutic Response in Chronic Graft-versus-Host Disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group Report

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Study Aims

1. Describe functional performance and capacity in allogeneic HSCT survivors with cGVHD
2. Characterize the extent of impairment in performance and capacity through comparisons with available normative values
3. Determine what variation in functional performance is explained by functional capacity, symptom bother, age, gender, comorbidity, cGVHD severity, intensity of immunosuppression, and time since cGVHD diagnosed

Design and Methods

- Cross-sectional, descriptive/correlational study
- Sample (n=100)
 - Older than 18
 - Able to speak, read and write English or Spanish
 - At least 100 days status post allogeneic hematopoietic stem cell transplantation
 - Diagnosis of chronic GVHD established through clinical signs and/or tissue biopsy of one or more organ systems

Measures

- **Symptom Bother**
 - Lee Chronic GVHD Symptom Scale
- **Functional Performance**
 - Medical Outcomes Study Short Form-36 (SF-36 v.2)
- **Functional Capacity**
 - 2 Minute Walk Distance, Grip Strength, Range of Motion
- **Demographic and Clinical Characteristics**

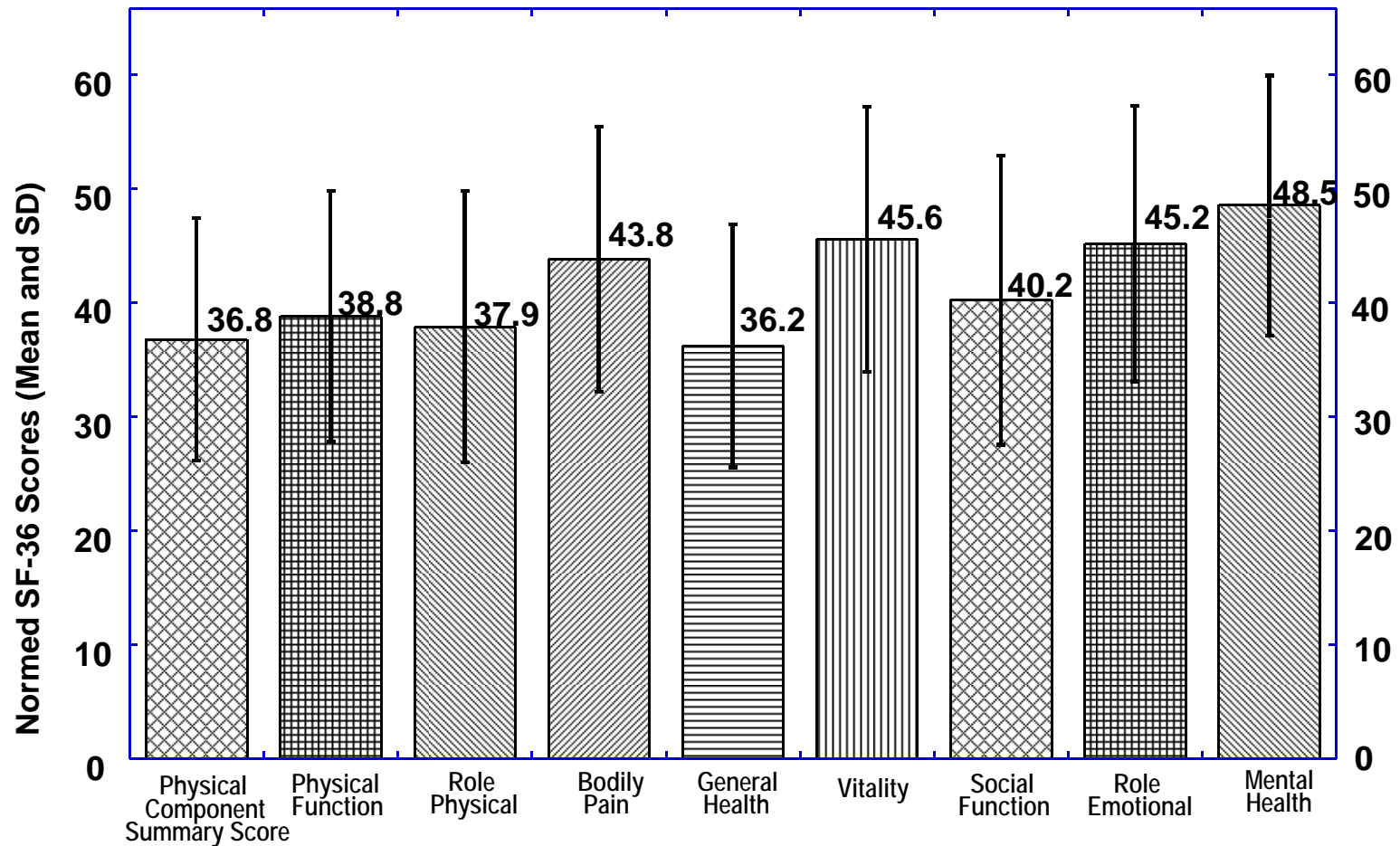
Sample Characteristics (N=100)

- Median age of 47 (range 20-66 years)
- 90% Caucasian; 66% married
- 42% working or going to school full-time
- 81% had undergone peripheral blood stem cell transplantation for a hematologic malignancy
- 68% received their graft from an HLA-matched sibling
- Mean of 42.6 months post transplant (range 4-201)
- Living with chronic GVHD for a mean of 35.6 months (range 1-196)

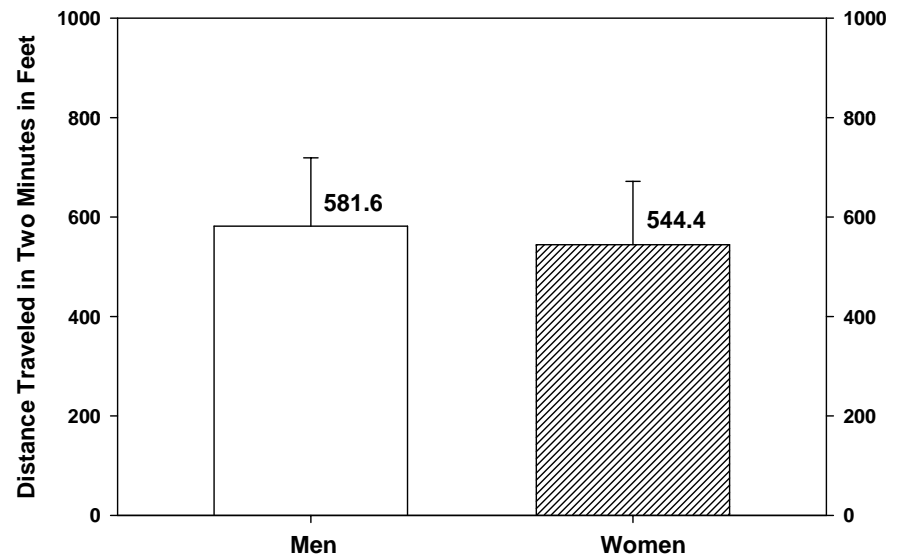
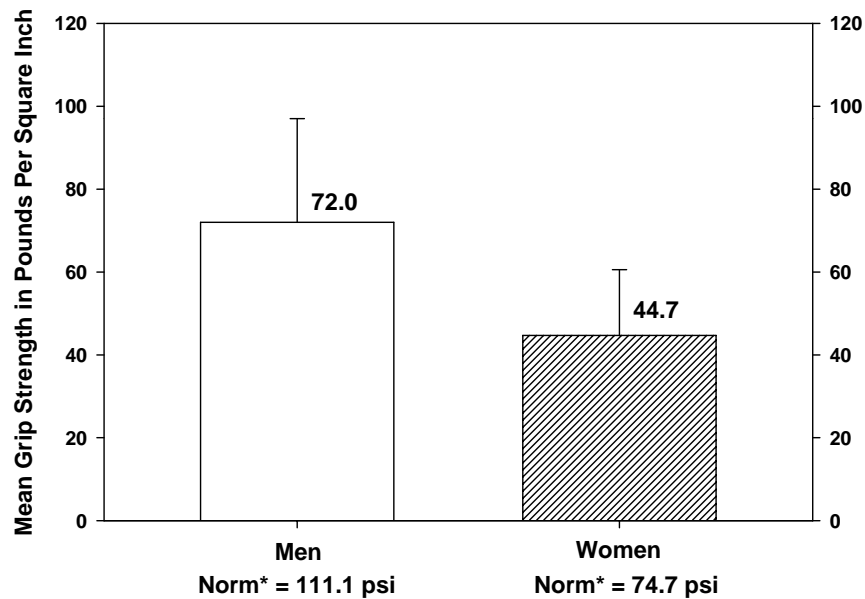
Sample Characteristics (N=100)

- 98% clinically extensive chronic GVHD
- Clinician-rated chronic GVHD composite severity score was mean of 31.7 (± 10.4) on a 0-100 scale
- 40% of the sample judged to have worsening chronic GVHD manifestations over the past month
- 75% on moderate or high levels of systemic immunosuppression
- 77% had a KPS $\geq 80\%$
- Median of two comorbidities; osteoporosis (48%), peripheral neuropathy (34%), depression (39%) and GERD (21%)
- 33% had a BMI less than 22, suggesting malnourishment

Functional Performance



Functional Capacity Grip Strength and Two Minute Walk Distance



Predictors of Functional Performance

Block	Variables in the model	β	Adj. R^2	$R^2\Delta$	F Δ	t
1	Demographic		0.0	0.01	0.1	
	Age	0.01				0.1
	Gender	-0.1				-0.2
2	Treatment		0.2	0.3	10.2**	
	cGVHD severity	-0.1				-1.6
	Intensity immunosupp.	-0.2				-2.2*
	Time since cGVHD Dx	0.1				0.7
3	Comorbidity	-0.1	0.3	0.1	14.0**	-1.6
4	Functional capacity		0.5	0.1	5.7**	
	Dist. walked in 2 min	0.4				4.6**
	Grip strength	0.01				0.1
	Upper body ROM	-0.1				-0.4
	Lower body ROM	0.1				0.4
5	Symptom bother	-0.4	0.55	0.1	17.2**	-4.1**

**Model
adjusted
 $R^2 = 0.55$;
 $F = 10.72$;
 $p < .001$**

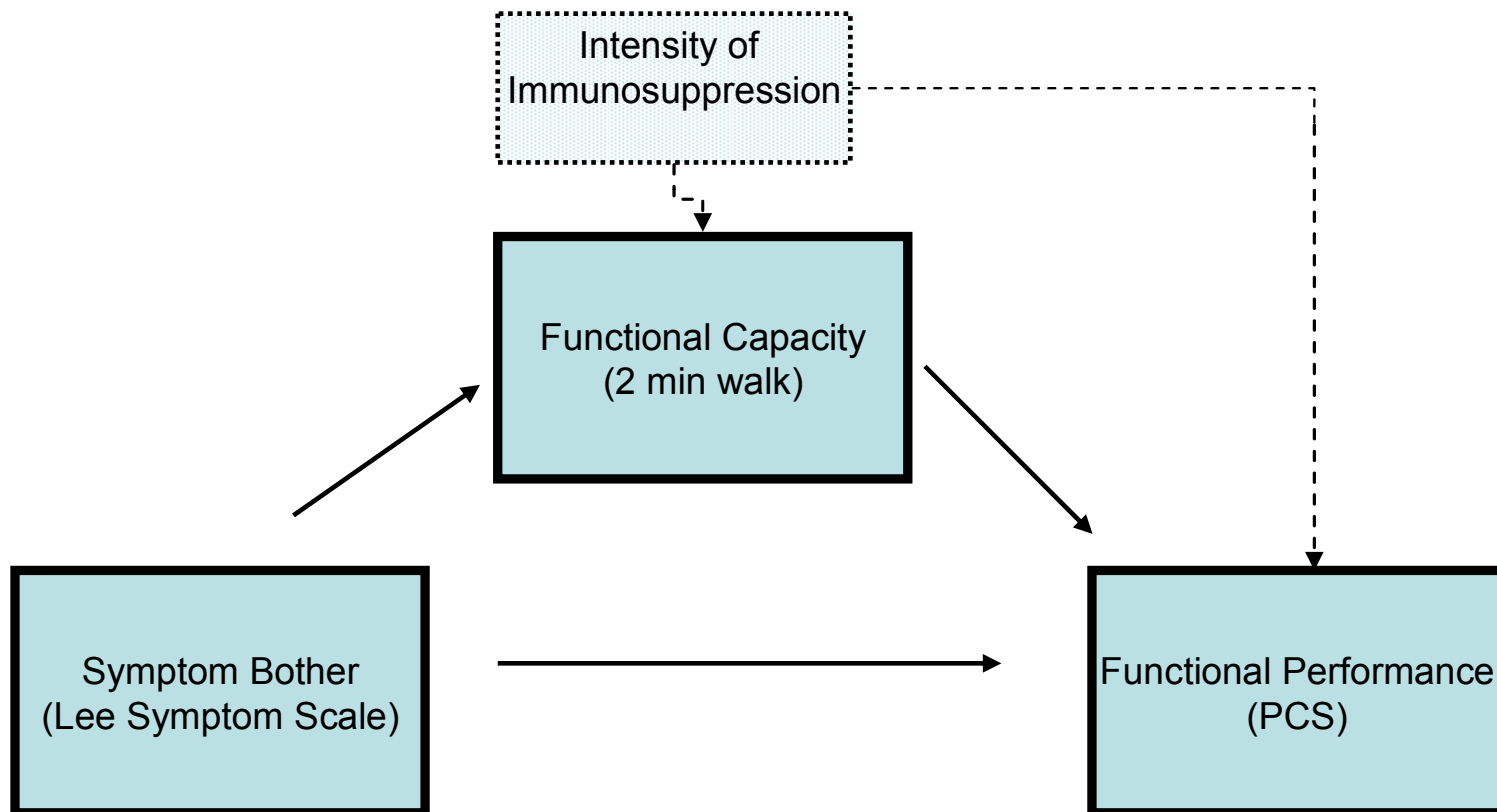
** $p < .01$ * $p < .05$

Predictors of Functional Performance

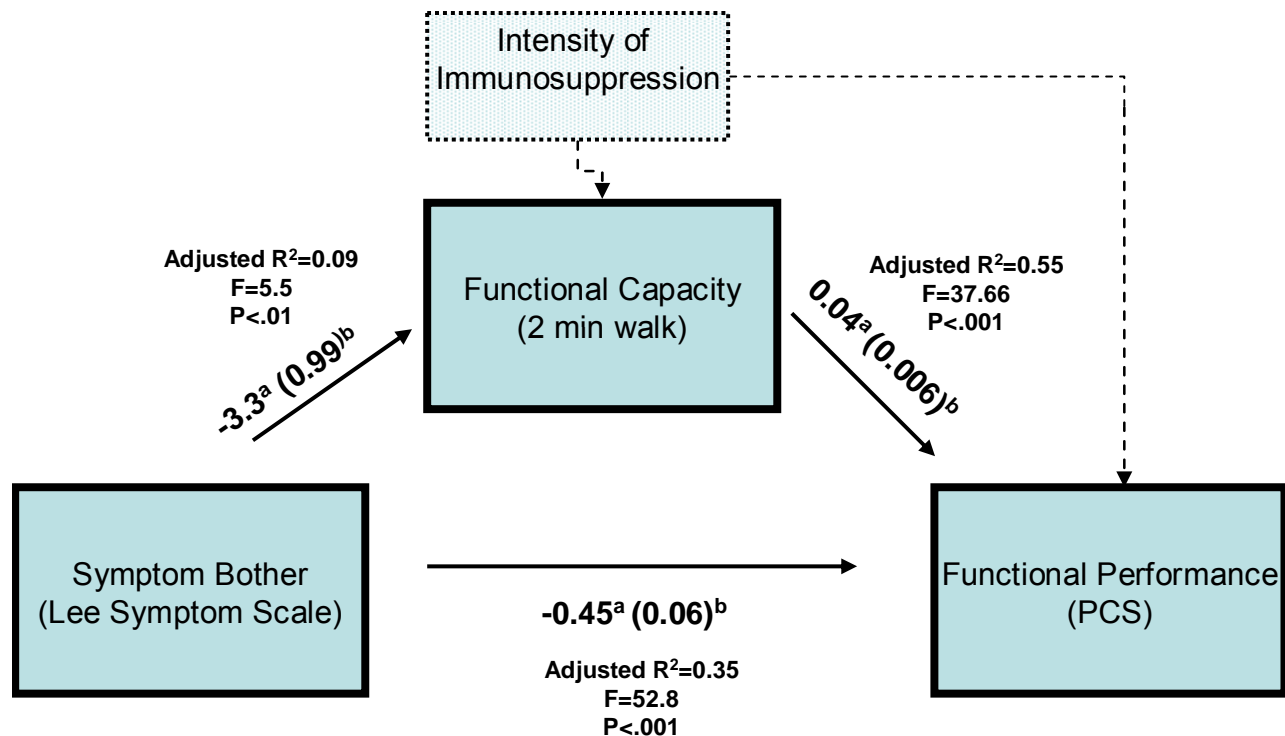
Variables in the model	β	Adj. R^2	$R^2\Delta$	F Δ	t
Final Model		0.56	0.58	40.46 ^{**}	
Intensity immunosuppression	-0.2				-2.5 ^{**}
Dist. walked in 2 min	0.5				6.3 ^{**}
Symptom bother	-0.4				-5.9 ^{**}

^{**} p<.001

Mediation Model



Functional Capacity Mediates the Relationship Between Chronic GVHD Symptom Bother and Functional Performance



^a Raw coefficient (β)

^b Standard error of raw coefficient (β)



Summary

- Functional performance was markedly impaired relative to normative values
 - >5 points lower on the physical component summary score and for all subscales except mental health
 - 70% of the sample had physical component summary scores that were significantly inferior to US population normative values
- A model with age, gender, chronic GVHD severity, intensity of immunosuppression, time since diagnosis, comorbidity, performance-based measures of functional capacity and symptom bother explained 55% of the variability in functional performance

Summary

- Intensity of immunosuppression, distance walked in 2 minutes and symptom bother were significant independent predictors (all $p < .001$) of functional performance
- Relationship between chronic GVHD symptom bother and functional performance was partially mediated by functional capacity

Limitations

- Psychometric properties of the measures of functional status in patients with cGVHD are unknown
- Collection of data at a single time point and in a sample of patients all of whom have chronic GVHD precludes dissection of the effects of chronic GVHD from persistent and late effects that result from high dose therapy
- Data were collected at a single site that is a national referral center for chronic GVHD

Implications for Survivorship Care

- Functional status is markedly impaired in this group of survivors
 - Periodic evaluation of both capacity and performance
 - Preventive and restorative rehabilitation measures
- Survivors receiving intensive immunosuppression are at particular risk for impairments in functional performance
 - Early preventive interventions
- Two-fold opportunity to improve functional performance:
 - Improve functional capacity (eg. muscle strength, ambulation)
 - Reduce chronic GVHD symptom

Measuring Functional Outcomes

- Two dimensions are required to capture the complexity of functional outcomes in chronic GVHD
- Results support inclusion of differing dimensions of function and contrasting methodologic approaches



Implications for Research

- Extend our findings through a longitudinal multi-site observational study designed to model the trajectory of symptoms and functional status from the time of early diagnosis of chronic GVHD
- Develop and test supportive care interventions:
 - Management of specific symptoms (eg. muscle/joint pain, weight loss)
 - Multi-component rehabilitative interventions shown in other chronically ill populations to reduce symptoms and improve functional capacity and self-management

Chronic GVHD Interdisciplinary Clinic and Study Group

- **Steven Pavletic, NCI, ETIB**

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