

# Failure-free survival in a prospective cohort of patients with chronic graft-versus-host disease

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Supplementary Table 1. Potential predictors of failure-free survival

<b>Organ</b>	<b>All variables Considered</b>	
<b>Skin</b>	Body surface area (BSA) individual measures (0-100)	
	Body surface area (BSA) summary measures (0-100)	
	Hopkins skin sclerotic score (0-4)	
	NIH skin score (0-3)	
	Hopkins fascia score (0-3)	
	Vienna skin score (VSS) individual measures (0-100)	
	Vienna skin score (VSS) summary measure (0-100)	
	Patient reported skin itching score (0-10)	
	Lee symptom skin summary (0-100)	
	Ulcer (yes vs. no)	
	Maculopapular rash (yes vs. no)	
	Lichen planus-like lesions (yes vs. no)	
	Poikiloderma (yes vs. no)	
	Pruritus (yes vs. no)	
	Keratosis pilaris (yes vs. no)	
	Papulosquamous lesions or ichthyosis (yes vs. no)	
	Hair involvement (yes vs. no)	
	Nail involvement (yes vs. no)	
	<b>Mouth</b>	NIH mouth score (0-3)
		Mouth erythema score (0-3)
Mouth lichenoid score (0-3)		
Mouth ulcers score (0-3)		
Mouth mucoceles score (0-3)		
Mouth pain score (0-3)		
Patient reported mouth dryness score (0-10)		
Patient reported mouth pain score (0-10)		
Patient reported mouth sensitivity score (0-10)		
Lee symptom mouth summary (0-100)		
<b>Eye</b>	Schirmer test result for each eye (0-35)	
	Average Schirmer test result (0-35)	
	Worst Schirmer test result (0-35)	
	NIH eye score (0-3)	
	Patient reported eye problem score (0-10)	
	Lee symptom eye summary (0-100)	
	Ocular surface disease index (OSDI) (0-100)	
<b>GI</b>	NIH GI score (0-3)	
	GI esophagus score (0-3)	
	Upper GI score (0-3)	
	Lower GI score (0-3)	
	Lee symptom nutrition summary (0-100)	
<b>Liver</b>	NIH liver score (0-3)	
	Total serum bilirubin (mg/dL)	

	ALT (units/L)
	Alkaline phosphatase (units/L)
	Albumin (mg/dL)
<b>Joint</b>	NIH joint score (0-3)
	Range of motion (ROM) shoulder score (0-7)
	Range of motion (ROM) elbow score (0-7)
	Range of motion (ROM) wrist score (0-7)
	Range of motion (ROM) foot score (0-4)
	Range of motion (ROM) summary (0-25)
<b>Lung</b>	FVC (%)
	FEV-1 (%)
	Adjusted single breath DLCO (%)
	Portable spirometer FEV-1 (%)
	Physician reported lung symptom score (0-3)
	NIH lung score (0-3)
	Lee symptom lung summary (0-100)
	Bronchiolitis obliterans syndrome (BOS) (yes vs. no)
	Bronchiolitis obliterans organizing pneumonia (BOOP) (yes vs. no)
<b>QOL</b>	FACT-BMT subscales
	SF-36 subscales
	Karnofsky performance status (0-100)
	Lee symptom psychological summary (0-100)
	Lee symptom energy summary (0-100)
<b>Functional</b>	Walk test result (feet)
	Grip test result (lbs)
	Human activity profile (HAP) maximum activity score (MAS)
	Human activity profile (HAP) adjusted activity score (AAS)
	Human activity profile (HAP) modified AAS
<b>Comorbidity</b>	Arrhythmia (yes vs. no)
	Coronary artery disease (yes vs. no)
	History of MI (yes vs. no)
	Heart valve disease (yes vs. no)
	Hypertension (yes vs. no)
	Congestive heart failure (yes vs. no)
	Cerebrovascular disease (yes vs. no)
	Peripheral vascular disease (yes vs. no)
	Venous thrombosis (yes vs. no)
	Peptic ulcer/hernia/reflux (yes vs. no)
	Mild hepatic (yes vs. no)
	Moderate/severe hepatic (yes vs. no)
	Inflammatory bowel disease (yes vs. no)
	Moderate pulmonary (yes vs. no)
	Severe pulmonary (yes vs. no)
	Asthma (yes vs. no)
	Diabetes (yes vs. no)
	Hypothyroidism (yes vs. no)
	Adrenal Insufficiency (yes vs. no)
	Psychiatric disturbance-Depression (yes vs. no)

	Psychiatric disturbance-Anxiety or panic disorder (yes vs. no)
	Neurologic disease (peripheral neuropathy, MS, Parkinson's disease or other chronic neurologic disease) (yes vs. no)
	Visual impairment secondary to cataracts, glaucoma or macular degeneration (yes vs. no)
	Hearing impairment (yes vs. no)
	Osteoarthritis (yes vs. no)
	Degenerative disc disease (spinal stenosis or severe chronic back pain) (yes vs. no)
	Avascular necrosis (yes vs. no)
	Osteopenia/Osteoporosis (yes vs. no)
	Rheumatologic (yes vs. no)
	Infection (yes vs. no)
	Moderate/severe renal (yes vs. no)
	Prior solid malignancy (yes vs. no)
<b>Overall</b>	Physician reported overall cGVHD severity score (0-3)
	Physician reported overall cGVHD severity score (0-10)
	Patient reported overall cGVHD severity score (0-3)
	Patient reported overall cGVHD severity score (0-10)
	Patient reported whether good control to decrease immunosuppressive medication (yes vs. no)
	Lee symptom overall summary (0-100)
<b>Lab</b>	Blood pressure (mm/Hg)
	WBC (k/uL)
	Platelet count (k/uL)
	Eosinophils (%)
	Neutrophils (%)
	Lymphocytes (%)
	Absolute lymphocyte count (k/uL)
	Creatinine (mg/dL)
	Glucose (mg/dL)
	Cholesterol (mg/dL)
	Triglycerides (mg/dL)
	LDL (mg/dL)
	HDL (mg/dL)
	Microalbumin (URN mg/g creatinine)
<b>Other</b>	Weight (kg)
	BMI (kg/m <sup>2</sup> )
	NIH genital score (0-3)
	Peripheral Edema (yes vs. no)
	Pleural effusions (yes vs. no)
	Nephrotic syndrome (yes vs. no)
	Malabsorption (yes vs. no)
	Esophageal stricture or web (yes vs. no)
	Ascites (yes vs. no)
	Myasthenia Gravis (yes vs. no)
	Peripheral Neuropathy (yes vs. no)
	Polymyositis (yes vs. no)
	Pericardial effusion (yes vs. no)

	Cardiomyopathy (yes vs. no)
	Cardiac Conduction defects (yes vs. no)
	Coronary artery involvement (yes vs. no)
<b>Transplant related</b>	Study site (FHCRC vs. other)
	Case type (incident vs. prevalent)
	Patient gender (female vs. male)
	Patient race (white vs. other)
	Months from transplant to enrollment(<12 vs. ≥12 months)
	Patient age at transplant (<50 vs. ≥50 years)
	Diagnosis (AML/ALL, CML/CLL, MDS, NHL/HD, other)
	Disease status (early, intermediate, advanced)
	Transplant source (bone marrow, cord blood, peripheral blood)
	Transplant type (myeloablative vs. non-myeloablative)
	Donor-patient CMV status (either positive vs. both negative)
	Donor match (matched related, matched unrelated, mismatched)
	Female donor into male recipient (yes vs. no)
	NIH Global severity (Mild or less, moderate, severe)
	GVHD type (overlap vs classic)
	Prior grade II-IV acute GVHD (yes vs. no)

Supplemental table 2: Univariable and Multivariable analyses of organ systems

Organ	Variables selected in univariable Cox models				Variables selected in multivariable Cox models for each organ			
	Variable	n	p-value	HR	Variable	n	p-value	HR
<b>Skin</b>	NIH skin score	555	<.001	1.23	NIH skin score	555	<.001	1.23
	Vienna skin score summary	554	<.001	1.06				
	BSA movable sclerosis summary	554	0.007	1.02				
	BSA non-movable sclerosis summary	554	0.003	1.02				
	Hopkins fascia score	555	0.001	1.30				

	Hopkins skin sclerotic score	555	0.007	1.17				
	Patient reported skin itching score	465	0.02	1.05				
	Lee symptom skin summary	473	0.001	1.01				
	Lichen planus-like lesions	551	0.01	1.44				
	Papulosquamous lesions or ichthyosis	555	0.007	2.11				
<b>Mouth</b>	NONE				NONE			
<b>Eye</b>	Schirmer test result left eye	418	0.008	0.99	Average Schirmer test result*	420	0.03	0.99
	Average Schirmer test result	420	0.03	0.99				
	Worst Schirmer test result	420	0.05	0.99				
<b>GI</b>	NIH GI score	555	0.05	1.17	NIH GI score	555	0.05	1.17
<b>Liver</b>	NIH liver score	553	0.01	1.15	NIH liver score (selected as calculated from bilirubin and alkaline phosphatase)	553	0.01	1.15
	Total serum bilirubin	550	0.03	1.06				
	Alkaline phosphatase	552	<.001	1.001				
<b>Joint</b>	NIH joint score	555	0.006	1.22	ROM summary	330	<.001	0.88
	ROM summary	330	<.001	0.88				
<b>Lung</b>	FVC	293	0.001	0.99	FVC	293	0.003	0.99

	FEV-1	293	0.001	0.99	BOS		0.01	2.02
	Portable spirometer FEV-1	484	0.007	0.99				
	Physician reported lung symptom score	555	0.004	1.29				
	BOS	554	0.01	1.83				
<b>QOL</b>	FACT BMT TOI	469	0.002	0.99	FACT TOI	469	0.002	0.99
	SF36 PCS	457	0.01	0.99				
	SF36 MCS	457	0.02	0.99				
	Karnofsky performance status	469	0.002	0.99				
	Lee symptom energy summary	472	0.02	1.01				
<b>Functional</b>	Walk test result	470	0.04	0.99	HAP modified AAS	472	0.02	0.99
	HAP AAS	472	0.01	0.99				
	HAP modified AAS	472	0.02	0.99				
<b>Comorbidity</b>	Peptic ulcer/hernia/reflux	553	0.01	0.75	Peptic ulcer/hernia/re flux	553	0.009	0.75
	Moderate/severe hepatic	553	0.05	1.45	Moderate/sev ere hepatic		0.05	1.50
<b>Overall</b>	Physician reported overall cGVHD severity score (0-3)	554	<.001	1.43	Physician reported overall cGVHD severity score (0-10)	550	<.001	1.12
	Physician reported overall cGVHD severity score (0-10)	550	<.001	1.12				
	Patient reported overall cGVHD severity score (0-3)	463	0.009	1.24				

	Patient reported overall cGVHD severity score (0-10)	461	<.001	1.10				
	Patient reported whether good control to decrease immunosuppressive medication	398	0.02	0.74				
	Lee symptom overall summary	474	0.01	1.01				
<b>Lab</b>	Platelet count	552	0.04	1.001	Platelet count	552	0.04	1.001
<b>Transplant</b>	Female donor into male recipient	551	0.03	1.27				
	NIH global severity	555	0.001	1.32				
	Prior grade II-IV acute GVHD	555	0.02	1.27				

\* Selected for the ease of interpretation

Abbreviations: HR, hazard ratio; NIH, National Institutes of Health; BSA, body surface area; GI, gastrointestinal; ROM, range of motion; FVC, forced vital capacity; FEV1, forced expiratory volume first second; BOS, bronchiolitis obliterans syndrome; FACT BMT TOI, functional assessment of cancer therapies bone marrow transplant subscale trial outcome index; SF36, short form 36; PCS, physical component score; MCS, mental component score; KPS, Karnofsky performance score; HAP, human activities profile; AAS, adjusted activity score; MD, clinician-reported score; PT, patient-reported score

## Supplementary Methods

Detailed description of statistical analysis: First, each collected variable was fit into a univariable Cox regression model (Supplementary Table 1). Second, within each organ system, factors associated with FFS with a univariable likelihood ratio test p-value  $\leq 0.05$  were then fit into a multivariable model for each organ. A backward elimination procedure was performed within each organ (Supplementary Table 2). Lastly, variables identified within each organ system were considered in building a multivariable Cox regression model across all organs (Table 3). A



backward elimination procedure was used to exclude risk factors until the p-value of the likelihood ratio test for all remaining risk factors was  $\leq 0.05$ . The final multivariable model included all statistically significant variables after backward elimination, as well as any statistically significant transplant characteristics. Global severity of chronic GVHD was predictive of FFS but was not included in the final multivariable model because it is derived from the organ-specific 0-3 scores, which were included as potential predictors.

New treatment was defined as a new immunosuppressive medication (for example, sirolimus, rituximab) or treatment (for example, extracorporeal photopheresis) intended for systemic treatment of chronic GVHD.<sup>(10)</sup> Specific doses of steroids were not accurately captured, but a pulse of high-dose solumedrol (i.e., 500 mg or 1000 mg) for several doses was considered as a treatment change. Topical therapies (e.g., topical steroids, ophthalmic cyclosporine, nonabsorbable steroids) supportive care treatments (e.g., ursodeoxycholic acid) and systemic non-immunosuppressive medications started for management of GVHD involving specific organs (e.g., montelukast or azithromycin for obstructive lung disease) were excluded.