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Characterization of Late Acute and Chronic Graft-Versus-Host Disease according to the 2014 National Institutes of Health Consensus Criteria in Japanese Patients

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A B S T R A C T

To characterize the incidences and outcomes of late acute (LA) and chronic graft-versus-host disease (GVHD) in East Asians according to the 2014 National Institutes of Health criteria, we retrospectively analyzed 506 consecutive Japanese patients who had a first allogeneic hematopoietic cell transplantation (HCT) at our center between 2006 and 2013. According to manifestations at onset 91 patients (60%) had LA GVHD and 60 (40%) had chronic GVHD. The cumulative incidences of LA and chronic GVHD were 20% and 17%, respectively, at 48 months after HCT. The involved sites at the onset of LA GVHD included the skin (71%), gut (13%), and liver (8%). The cumulative incidences of relapse, nonrelapse mortality (NRM), transition to chronic GVHD, and discontinued systemic treatment were 11%, 6%, 22%, and 46%, respectively, at 48 months after onset of LA GVHD. Cox models showed that prior acute GVHD was associated with NRM, and HCT from a female donor to a male patient, myeloablative conditioning, and low Karnofsky performance status were associated with a longer duration of systemic treatment after LA GVHD. The most frequently involved sites at the onset of chronic GVHD included the mouth (83%), liver (75%), skin (69%), and eyes (62%). Cox models showed that use of antithymocyte globulin in conditioning regimens was associated with a higher risk of discontinued systemic treatment after the onset of chronic GVHD. The cumulative incidences of relapse, NRM, and discontinued systemic treatment were 16%, 11%, and 41%, respectively, at 48 months after the onset of chronic GVHD. Our results suggested several potential differences between Japanese patients and those of other ethnicities. A direct comparison is needed to formally investigate ethnic differences.

INTRODUCTION

Chronic graft-versus-host-disease (GVHD) occurs in 30% to 70% of patients after allogeneic hematopoietic cell transplantation (HCT) and is the major cause of late morbidity and mortality [1]. In the past GVHD was classified according to the duration of onset after HCT [2]. GVHD that occurred within 100 days after HCT was classified as acute GVHD and that occurred beyond 100 days was classified as chronic GVHD. Since the National Institutes of Health (NIH) consensus criteria were established in 2005, chronic GVHD has been classified into late acute (LA) GVHD and NIH chronic GVHD by clinical manifestations rather than onset time [3].

Several studies have characterized chronic GVHD defined by the NIH consensus criteria. Arora et al. [4] showed that the cumulative incidences of LA GVHD and NIH chronic GVHD at 2 years were 10% and 47%, respectively. Vigorito et al. [5] showed that 48% of historical chronic GVHD met the criteria of NIH chronic GVHD, and the probabilities of survival, nonrelapse mortality (NRM), recurrent malignancy, and discontinued systemic treatment did not differ statistically between patients with LA GVHD and those with NIH chronic GVHD.

Revisions of the 2005 NIH consensus criteria were made in 2014 to address areas of controversy and confusion [6,7]. The diagnostic criteria for involvement of the mouth, lungs, and genitalia were revised [7]. Previous studies of chronic GVHD using the 2005 NIH consensus criteria examined mostly white patients [5,8,9], but few studies examined East Asians [10,11], who are genetically more homogeneous than other ethnicities and are likely to have different GVHD characteristics and outcomes [12,13]. The aim of this study was to elucidate the characteristics and outcomes of LA and chronic GVHD among Japanese patients using the 2014 NIH consensus criteria.

METHODS

Patient and Data Collection

The study cohort included 506 consecutive patients who had a first allogeneic HCT at the National Cancer Center Hospital between January 2006 and October 2013. GVHD was retrospectively classified as LA GVHD or chronic

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GVHD according to the 2014 NIH consensus criteria [7]. This study was approved by the institutional review board of the National Cancer Center and was conducted in accordance with the Declaration of Helsinki.

Definitions

Acute GVHD was defined by the 1994 consensus criteria [14]. Diagnosis of LA and chronic GVHD was made by the 2014 NIH consensus criteria [7]. LA GVHD was classified as recurrent if there was a recurrence of acute GVHD after day 100, de novo if acute GVHD presented after day 100 for the first time, or persistent if acute GVHD continued across day 100. Except for the lungs, organ involvement with chronic GVHD was defined as an NIH organ score ≥ 1. Lung involvement was defined for patients with bronchiolitis obliterans syndrome according to the 2014 NIH consensus criteria. Liver staging was based on serum total bilirubin values for LA GVHD and was based on values of serum total bilirubin, alanine aminotransferase, and alkaline phosphatase for NIH chronic GVHD. Relapse was defined by either morphologic or cytogenetic evidence of disease recurrence or radiologic evidence of recurrent or progressive disease. NRM was defined as death without recurrent malignancy. Discontinued systemic treatment was defined as the discontinuation and subsequent lack of systemic immunosuppressive treatment for at least 6 months. HLA matching for sibling and cord blood donors was assessed by serologic data at the HLA-A, -B, and -DR loci. HLA matching for unrelated donors was assessed using allele data at the HLA-A, -B, -C, and -DRB1 loci. The intensity of conditioning regimens was previously defined [15].

Statistical Analysis

Categorical variables were compared using Fisher's exact test. Continuous variables were compared using the Mann-Whitney test. Cumulative incidences of LA GVHD, NIH chronic GVHD, and discontinued systemic treatment were calculated by Gray's method. In the analysis of GVHD, relapse and death before onset of GVHD were considered as competing events. In the analysis of discontinued systemic treatment after LA GVHD, relapse, NRM, and

Table 1
Patient Characteristics

Characteristic	LA Onset (n = 91)		NIH Chronic Onset (n = 60)		*P*
Median patient age, yr (range)	46	(15-68)	49	(18-68)	.56
Sex					.40
Male	58	(64)	34	(57)	
Female	33	(36)	26	(43)	
Disease					.28
AML/MDS	46	(51)	31	(52)	
ALL	13	(14)	3	(5)	
ML	30	(33)	25	(42)	
Others	2	(2)	1	(2)	
Donor type					.17
Related	52	(57)	27	(45)	
Unrelated	39	(43)	33	(55)	
HLA matching					.13
Match	52	(57)	42	(70)	
Mismatch	39	(43)	18	(30)	
Donor–patient gender combination					.17
Female donor to male patient	25	(27)	10	(17)	
Others	66	(73)	50	(83)	
Conditioning intensity					.40
Myeloablative	47	(52)	28	(47)	
Reduced intensity	44	(48)	32	(53)	
TBI in conditioning regimen	39	(43)	27	(45)	.61
ATG in conditioning regimen	11	(12)	4	(7)	.40
Stem cell source					.23
Bone marrow	61	(67)	34	(57)	
Mobilized blood	27	(30)	26	(43)	
Cord blood	3	(3)	0	(0)	
Prior grades II-IV acute GVHD	48	(53)	19	(32)	.01
Year of transplantation					.62
2006-2009	43	(47)	31	(52)	
2010-2013	48	(53)	29	(48)	

Values are n (%) unless otherwise defined. AML indicates acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; ML, malignant lymphoma; TBI, total body irradiation; ATG, antithymocyte globulin.

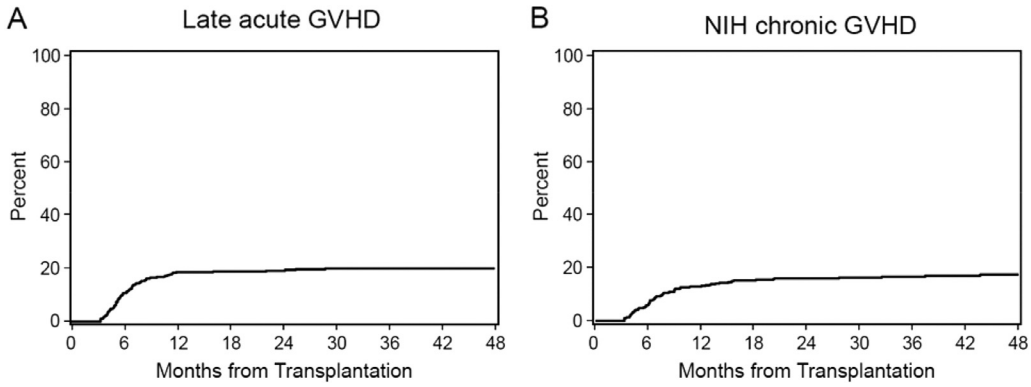

Figure 1. Cumulative incidences of (A) LA GVHD and (B) NIH chronic GVHD.

transition to NIH chronic GVHD were considered as competing events. In the analysis of discontinued systemic treatment after NIH chronic GVHD, relapse and NRM were considered as competing events.

Cox proportional hazard regression models were used to examine risk factors associated with overall mortality. Fine-Gray proportional hazard models were used to examine risk factors associated with NRM, relapse, and discontinued systemic treatment. Covariates included patient age, primary disease type, donor type, HLA matching, donor–patient gender combination, conditioning intensity, total body irradiation in conditioning regimens, antithymocyte globulin in conditioning regimens, stem cell source, prior acute GVHD, year of HCT, type of GVHD onset, category of GVHD, number of involved sites at onset, Karnofsky performance status at onset, steroid use at onset, thrombocytopenia (<100,000/μL) at onset, hyperbilirubinemia (>2 mg/dL) at onset, grade of LA GVHD at onset, and global score of NIH chronic GVHD at onset.

Factors having $P < .1$ in univariate analysis were included in multivariate models. Two-sided $P < .05$ was considered statistically significant. All statistical analyses were performed with STATA 12.1 (StataCorp, College Station, TX) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), the latter of which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [16].

RESULTS

Patient Characteristics

Among the 506 consecutive patients who had a first allogeneic HCT at the National Cancer Center Hospital during the study period, 151 patients without recurrent malignancy developed extensive chronic GVHD requiring systemic treatment. The cumulative incidence of extensive chronic GVHD was 33% (95% confidence interval [CI], 29% to 37%) at 48 months after HCT. According to manifestations at onset, 91 patients (60%) had LA GVHD and 60 patients (40%) had NIH chronic GVHD. The median follow-up duration among survivors was 41 months (range, 5.6 to 99) after onset of extensive chronic GVHD.

Patient characteristics according to onset type of GVHD are summarized in Table 1. The median patient age was 48 years (range, 15 to 68). There were 92 male patients (61%) and 59 female patients (39%). Fifty-seven patients (37%) had HLA mismatching, 35 male patients (23%) had HCT from a female donor, 15 (10%) had antithymocyte globulin as GVHD prophylaxis, and 53 (63%) had mobilized blood cells. Patient characteristics did not differ statistically between patients with LA onset and those with NIH chronic onset, except for prior history of acute GVHD. Prior history of grades II to IV acute GVHD was more frequent in patients with LA onset than those with NIH chronic onset.

Table 2
Characteristics of LA GVHD at Onset (n = 91)

Characteristic	Value
Median time from transplantation to diagnosis, mo (range)	5.8 (3.3-29)
Category of LA GVHD	
Late onset	35 (38)
Recurrent	46 (51)
Persistent	10 (11)
Involved site	
Skin	65 (71)
Liver*	7 (8)
Gastrointestinal tract	12 (13)
Grade of LA GVHD	
Grade I	54 (59)
Grade II	26 (29)
Grade III	11 (12)
Grade IV	0 (0)
Number of involved sites	
1	81 (89)
2	10 (11)
3	0 (0)
Karnofsky performance status < 80%	22 (24)
Dose of prednisone at onset	
None	76 (84)
>0 but <.5 mg/kg	13 (14)
.5-1 mg/kg	2 (2)
>1 mg/kg	0 (0)
Thrombocytopenia (< 100,000/μL)	32 (35)
Hyperbilirubinemia (> 2 mg/dL)	5 (5)

Values are n (%) unless otherwise defined.
* When liver involvement was defined according to the 2014 NIH liver score that incorporated serum total bilirubin, alanine aminotransferase, and alkaline phosphatase, liver was involved in 49 patients (54%).

Late Acute GVHD

Ninety-one patients developed LA GVHD. The cumulative incidence of LA GVHD was 20% (95% CI, 16% to 24%) at 48 months after HCT (Figure 1A). Characteristics of LA GVHD are summarized in Table 2. The median interval from HCT to onset of LA GVHD was 5.8 months (range, 3.3 to 29). Thirty-five patients (38%) had late-onset type, 46 (51%) had recurrent

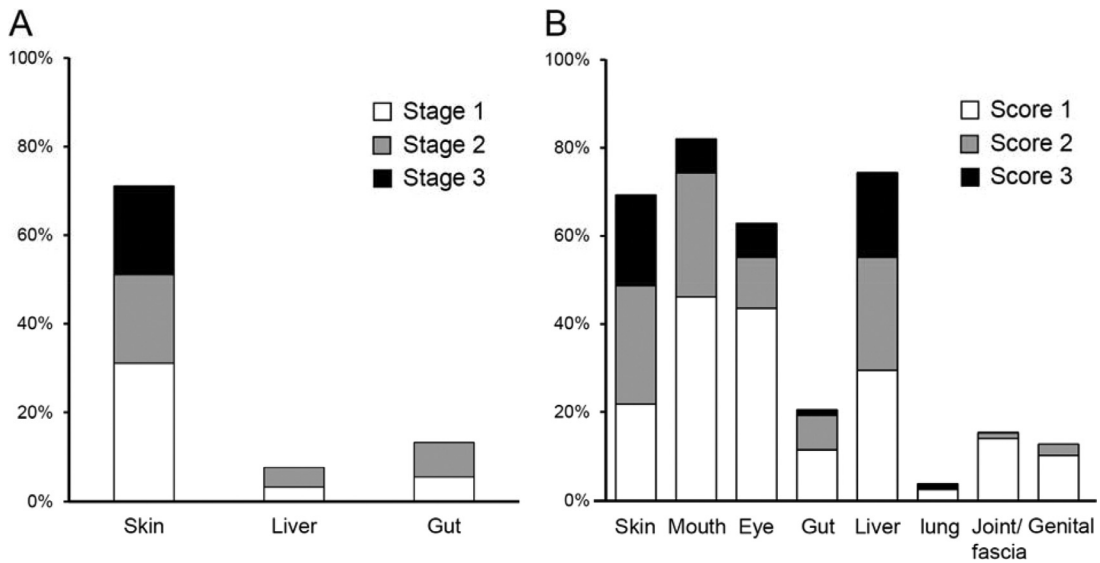

Figure 2. Organ scores at onset of (A) LA GVHD and (B) NIH chronic GVHD.

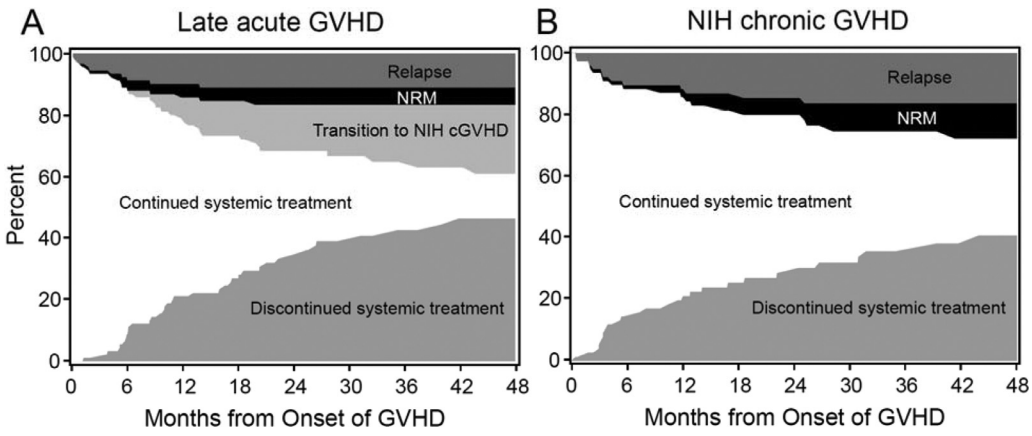

Figure 3. Outcomes after onset of (A) LA GVHD and (B) NIH chronic GVHD. Each area represents probabilities of relapse, NRM, transition to NIH chronic GVHD, continued systemic treatment, and discontinued systemic treatment.

Table 3
Risk Factors associated with Outcomes after Onset of LA GVHD

	NRM				Discontinuation of Systemic Treatment			
	Univariate		Multivariate		Univariate		Multivariate	
Factor at Onset	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Patient age, per year	1.00 (.95-1.05)	.93			1.02 (.99-1.05)	.18		
Disease								
AML/MDS	1.00 (reference)				1.00 (reference)			
ALL	1.19 (.13-10.8)	.88			1.25 (.49-3.19)	.64		
ML	.51 (.05-4.91)	.56			1.08 (.55-2.11)	.82		
Others	NA	NA			NA	NA		
Donor type								
Related	1.00 (reference)				1.00 (reference)			
Unrelated	.73 (.12-4.30)	.72			1.56 (.76-3.20)	.23		
HLA matching								
Match	1.00 (reference)				1.00 (reference)			
Mismatch	1.15 (.20- 6.70)	.87			.61 (.33-1.14)	.12		
Female donor to a male patient	1.78 (.30-6.70)	.52			.32 (.12-.83)	.019	.30 (.12-.78)	.013
Conditioning intensity								
Myeloablative	1.00 (reference)				1.00 (reference)		1.00 (reference)	
Reduced intensity	.40 (.03-2.50)	.27			2.39 (1.24-4.58)	.009	2.05 (1.03-4.08)	.041
TBI in conditioning regimen	.89 (.15-5.30)	.90			1.10 (.59-2.06)	.76		
ATG in conditioning regimen	1.78 (.22-14.6)	.59			1.93 (.91-4.07)	.09	1.00 (.44-2.32)	.99
Stem cell source								
Bone marrow	1.00 (reference)				1.00 (reference)			
Mobilized blood	.55 (.06-4.94)	.60			1.01 (.50-2.06)	.97		
Cord blood	NA	NA			2.94 (.68-12.8)	.15		
Prior acute GVHD, per grade	7.50 (2.09-26.9)	.002	6.06 (2.41-15.2)	<.001	1.38 (.69-2.76)	.36		
Year of transplantation								
2006-2009	1.00 (reference)				1.00 (reference)			
2010-2013	.60 (.10-3.53)	.58			1.02 (.55-1.91)	.94		
Category of LA GVHD								
Late onset	NA	NA			.77 (.41-1.42)	.41		
Recurrent	1.00 (reference)				1.00 (reference)			
Persistent	3.47 (.58-2.08)	.17			.67 (.19-2.36)	.53		
Onset grade of LA GVHD								
Grade I	1.00 (reference)				1.00 (reference)			
Grades II-IV	6.06 (.67-54.1)	.11			1.15 (.61-2.17)	.67		
Number of involved sites								
1	1.00 (reference)				1.00 (reference)			
2-3	.47 (.05-4.15)	.50			1.09 (.56-2.12)	.79		
Karnofsky performance status								
80-100%	1.00 (reference)		1.00 (reference)		1.00 (reference)			
<80%	5.05 (.88-29.0)	.07	.94 (.33-2.65)	.91	.34 (.12-.97)	.044	.35 (.12-1.00)	.05
Steroid use	8.04 (1.37-47.2)	.02	3.49 (.85-14.4)	.08	.97 (.92-1.01)	.14		
Thrombocytopenia (<100,000/μL)	2.76 (.45-17.1)	.28			.63 (.31-1.27)	.20		
Hyperbilirubinemia (>2 mg/dL)	NA	NA			.39 (.05-3.17)	.38		

NA indicates not applicable.

type, and 10 (11%) had persistent type. Organ stage at onset of LA GVHD is shown in Figure 2A. The most frequently involved site was the skin (71%), followed by the gut (13%) and liver (8%). When liver involvement was defined according to the NIH liver score, which incorporates serum total bilirubin, alanine aminotransferase, and alkaline phosphatase, the liver involvement rate increased to 54%. The onset grades of LA GVHD were grade I in 54 patients (59%), grade II in 26 (29%), and grade III in 11 (12%). Eighty-one patients (89%) had involvement of a single organ at onset. Seventy-six patients (84%) were not taking a steroid at the onset of LA GVHD. Thirty-two patients (35%) had thrombocytopenia and 5 (5%) had hyperbilirubinemia at the onset of LA GVHD. Seventeen patients subsequently developed NIH chronic GVHD.

Outcomes after onset of LA GVHD are illustrated in Figure 3A. The cumulative incidences of relapse, NRM, transition to NIH chronic GVHD, and discontinuation of systemic treatment were 11% (95% CI, 6% to 18%), 6% (95% CI, 2% to 12%), 22% (95% CI, 14% to 32%), and 46% (95% CI, 35% to 57%), respectively, at 48 months after onset of LA GVHD. The median duration of systemic treatment among patients who discontinued systemic treatment was 11 months (range, 1.2 to 42). The onset of LA GVHD was not statistically associated with the risk of subsequent recurrent malignancy in time-dependent analysis (hazard ratio [HR], .77; 95% CI, .42 to 1.39; $P = .38$).

We next examined risk factors associated with NRM and discontinued systemic treatment after onset of LA GVHD (Table 3). In univariate analysis prior acute GVHD and steroid use at onset of LA GVHD were associated with an increased risk of NRM. Only prior acute GVHD remained statistically significant in the multivariate analysis. In univariate analysis HCT from a female donor to a male patient and Karnofsky performance status < 80% were associated with a lower risk of discontinued systemic treatment, and reduced-intensity conditioning was associated with a higher risk of discontinued systemic treatment. These 3 factors remained statistically significant in multivariate analysis.

NIH Chronic GVHD

Seventy-seven patients developed NIH chronic GVHD. The cumulative incidence of NIH chronic GVHD was 17% (95% CI, 14% to 21%) at 48 months after HCT (Figure 1B). Characteristics of NIH chronic GVHD are summarized in Table 4. The median interval from HCT to onset of NIH chronic GVHD was 5.8 months (range, 3.3 to 16). Forty-one patients (53%) had de novo onset, 30 (39%) had quiescent onset, and 6 (8%) had progressive onset. Eleven patients (14%) had classic chronic GVHD and 66 (86%) had overlap syndrome. The NIH organ scores at onset of NIH chronic GVHD are shown in Figure 2B. The most frequently involved sites included the mouth (83%), liver (75%), skin (69%), and eyes (62%). Among 15 patients (19%) with an overall lung score ≥ 1, 3 (4%) met the 2014 NIH criteria for bronchiolitis obliterans syndrome. The global score was mild in 5 patients (7%), moderate in 35 (45%), and severe in 37 (48%). Thirty-nine patients (51%) had involvement of ≥4 organs at onset. Most patients (83%) were not taking a steroid at onset of NIH chronic GVHD. Twenty-nine patients (38%) had thrombocytopenia, and 2 (3%) had hyperbilirubinemia at onset of NIH chronic GVHD.

Outcomes after onset of NIH chronic GVHD are illustrated in Figure 3B. The cumulative incidences of relapse, NRM, and discontinued systemic treatment were 16% (95% CI, 9% to 26%), 11% (95% CI, 5% to 21%), and 41% (95% CI, 28% to 53%), respectively, at 48 months after onset of NIH chronic GVHD. The median duration of systemic treatment among patients who discontinued systemic treatment was 11 months (range, .5 to 44). The onset of NIH chronic GVHD was not statistically associated with the risk of subsequent recurrent malignancy in time-dependent analysis (HR, 1.32; 95% CI, .76 to 2.31; $P = .32$).

Table 4
Characteristics of NIH Chronic GVHD at Onset (n = 77)

Characteristic	Value
Median time from transplantation to diagnosis, mo (range)	5.8 (3.3-16)
Type of onset	
De novo	41 (53)
Quiescent	30 (39)
Progressive	6 (8)
Category of chronic GVHD	
Classic	11 (14)
Overlap	66 (86)
Involved site	
Skin	53 (69)
Eyes	48 (62)
Mouth	64 (83)
Liver	58 (75)
Lung	3 (4)
Gastrointestinal tract	15 (19)
Joint	12 (16)
Genital	10 (13)
Global score	
Mild	5 (7)
Moderate	35 (45)
Severe	37 (48)
Number of involved sites	
1 or 2	25 (32)
3	13 (17)
4 or more	39 (51)
Karnofsky performance status < 80%	21 (27)
Dose of prednisone at onset	
None	64 (83)
>0 but <.5 mg/kg	12 (16)
.5-1 mg/kg	1 (1)
>1 mg/kg	0 (0)
Thrombocytopenia (<100,000/μL)	29 (38)
Hyperbilirubinemia (>2 mg/dL)	2 (3)

Values are n (%) unless otherwise defined.

We next examined risk factors associated with NRM and discontinued systemic treatment after onset of NIH chronic GVHD (Table 5). No factor was statistically associated with the risk of NRM. The use of antithymocyte globulin in the conditioning regimen was associated with a higher risk of discontinued systemic treatment (HR, 3.29; 95% CI, 1.13 to 9.58; $P = .029$).

Comparison of Outcomes between LA GVHD and NIH Chronic GVHD according to Onset Type

Outcomes between LA GVHD and NIH chronic GVHD were compared according to onset type (Table 6). Risks of NRM, recurrent malignancy, overall mortality, and discontinued systemic treatment did not differ statistically according to onset type.

DISCUSSION

We retrospectively classified extensive chronic GVHD in Japanese patients as LA GVHD or NIH chronic GVHD according to the 2014 NIH criteria. According to manifestations at onset 60% of cases were classified as LA GVHD and 40% as NIH chronic GVHD in this study. The proportion of patients with LA onset has varied in previous studies, ranging from 15% to 47% in studies of mostly white patients [5,8,9] compared with 63% in a Korean study [10], a value that was similar to ours. Ethnic differences might account for the higher proportion of LA GVHD in the present study and the Korean study.

The cumulative incidence of LA GVHD was 20% at 2 years after HCT in this study and was higher than 10% to 14% in

Table 5
Risk Factors associated with Outcomes after Onset of NIH Chronic GVHD

	NRMUnivariate		Discontinuation of Systemic TreatmentUnivariate	
Factor at Onset	HR (95% CI)	*P*	HR (95% CI)	*P*
Patient age, per year	1.01 (.96-1.06)	.68	1.00 (.97-1.03)	.84
Disease				
AML/MDS	1.00 (reference)		1.00 (reference)	
ALL	NA	NA	1.12 (.28-4.44)	.88
ML	.39 (.08-1.91)	.25	1.10 (.50-2.40)	.81
Others	NA	NA	4.49 (.30-66.2)	.27
Donor type				
Related	1.00 (reference)		1.00 (reference)	
Unrelated	1.42 (.35-5.86)	.63	1.83 (.86-3.93)	.12
HLA matching				
Match	1.00 (reference)		1.00 (reference)	
Mismatch	1.74 (.42-7.11)	.44	1.86 (.40-1.85)	.70
Female donor to male patient	1.83 (.50-6.67)	.36	.57 (.20-1.64)	.30
Conditioning intensity				
Myeloablative	1.00 (reference)		1.00 (reference)	
Reduced intensity	.54 (.14-2.06)	.37	1.37 (.65-2.89)	.41
TBI in conditioning regimen	4.15 (.89-19.3)	.07	.76 (.35-1.62)	.47
ATG in conditioning regimen	NA	NA	3.29 (1.13-9.58)	.029
Stem cell source				
Bone marrow	1.00 (reference)		1.00 (reference)	
Mobilized blood	.80 (.19-3.36)	.76	.53 (.24-1.16)	.11
Prior acute GVHD (per grade)	1.25 (.69-2.31)	.46	.86 (.30-2.48)	.36
Year of transplantation				
2006-2009	1.00 (reference)		1.00 (reference)	
2010-2013	1.33 (.37-4.80)	.65	1.26 (.53-2.67)	.55
Type of onset				
De novo	1.00 (reference)		1.00 (reference)	
Quiescent	1.59 (.38-6.68)	.53	1.67 (.30-1.47)	.32
Progressive	2.24 (.26-19.0)	.46	.90 (.17-4.68)	.90
Category of chronic GVHD				
Classic	1.00 (reference)		1.00 (reference)	
Overlap	NA*	NA	.66 (.26-1.64)	.37
Global score				
Mild or moderate	1.00 (reference)		1.00 (reference)	
Severe	2.23 (.60-8.32)	.23	.86 (.41-1.81)	.69
Number of involved site				
1 or 2	1.00 (reference)		1.00 (reference)	
3	1.98 (.12-31.9)	.63	.80 (.29-2.22)	.68
4 or more	3.50 (.43-28.1)	.24	.55 (.24-1.26)	.16
Karnofsky performance status				
80-100	1.00 (reference)		1.00 (reference)	
0-70	2.20 (.59-8.16)	.24	.79 (.35-1.81)	.59
Steroid use	1.98 (.41-9.47)	.39	.87 (.30-2.48)	.79
Thrombocytopenia (<100,000/μL)	.84 (.23-3.17)	.81	.76 (.34-1.67)	.50
Hyperbilirubinemia (>2 mg/dL)	NA	NA	1.43 (.54-3.83)	.48

* The result is not available because no patients with classic chronic GVHD had NRM.

previous studies [4,17,18]. One reason is that our cohort included patients with persistent LA GVHD, whereas some studies did not [4,18]. The proportion of patients with late onset was higher in this study than in others [5,9,10,17]. Among 35 patients with late-onset LA GVHD in this study, none had NRM. A previous study by Omer et al. [17] reported a low NRM rate because of a higher durable treatment response rate in late-onset LA GVHD than in other subtypes.

Most patients (95%) in this study had 1 or 2 involved sites at onset of LA GVHD, consistent with a previous report [5]. The proportion of gut involvement was lower compared with previous studies [5,18]. The rate of discontinued systemic treatment appeared to be higher and the incidence of NRM appeared to be lower than in a previous study that included mostly white patients [5]. A direct comparison is necessary to draw definitive conclusions, but Japanese patients with LA GVHD might have a better prognosis than white patients because of their lower incidence of gastrointestinal involvement. Based on these results, treatment with low-dose corticosteroids and topical agents such as steroid ointment for skin may be considered in Japanese patients with LA GVHD.

A higher grade of prior acute GVHD was associated with a higher risk of NRM after onset of LA GVHD. No previous study has identified this association. HCT from a female donor to a male patient and myeloablative conditioning were associated

Table 6
Outcomes of NIH Chronic GVHD Compared with LA GVHD according to Onset Type

Outcome	HR* (95% CI)	*P*
NRM	2.08 (.73-5.88)	.17
Recurrent malignancy	1.68 (.78-3.63)	.19
Overall mortality	1.51 (.78-2.92)	.22
Discontinuation of systemic treatment	.86 (.52-1.44)	.57

* Models accounting for transition from LA GVHD to NIH chronic GVHD as a competing event. Results were similar with models not accounting for transition from LA GVHD to NIH chronic GVHD.

with a lower risk of discontinued systemic treatment after onset of LA GVHD. Previous studies reported that HCT from a female donor to a male patient [19-22] and myeloablative conditioning [23] were associated with an increased risk of severe acute GVHD that might result in prolongation of systemic treatment.

The cumulative incidence of NIH chronic GVHD was 17% at 2 years after HCT in this study, which was lower than the generally recognized rate of 30% to 50% in white patients [24]. Oh et al. [12] reported a lower rate of acute GVHD and historical chronic GVHD in Japanese patients than in other ethnicities. Kuwatsuka et al. [25] also reported that the risk of historical chronic GVHD in Japanese patients was lower than in white patients in a contemporary registry cohort.

The proportions of onset types of NIH chronic GVHD have varied in previous reports [4,5,8,26], but the frequency of progressive onset has been consistently low in all studies, including the current one. Compared with a previous study [5], this study demonstrated a larger number of involved sites in chronic GVHD, with more than half of patients having 4 or more involved sites. As in prior studies the most frequently involved sites were the skin, mouth, and eyes [4,5,27,28]. Notably, the proportion of patients with liver involvement (75%) was higher in this study than in previous studies, which might represent an ethnic difference. One multicenter observational study that included mostly white patients reported a 50% lung involvement rate based on the 2005 NIH lung score for defining lung involvement [29], whereas the rate was 19% in this study, which used the 2014 NIH lung score. When we defined lung GVHD as clinical bronchiolitis obliterans syndrome, the rate was 4% at onset of chronic GVHD, and a similar rate was observed in another retrospective study of mostly white patients [27].

Compared with previous studies our cohort included many patients with severe global scores, which were the result of involvement of the skin (43%), liver (38%), lungs (16%), eyes (16%), and mouth (14%). In a study of white patients severe global scores most frequently resulted from involvement of the lungs (45%), skin (36%), eyes (25%), mouth (15%), liver (12%), and joints or fascia (11%) [29].

Compared with the study by Vigorito et al. [5], which included mostly white patients, our study showed a similar probability of discontinued systemic treatment after treatment for chronic GVHD, and the probability of NRM was lower in this study despite the larger proportion of patients with severe chronic GVHD. This may indicate an ethnic difference in treatment outcomes of chronic GVHD, possibly due to different sites contributing to severe global scores. The risks of NRM, recurrent malignancy, overall mortality, and discontinued systemic treatment did not differ statistically between LA GVHD and NIH chronic GVHD according to onset type, a result that was consistent with Vigorito et al.'s study [5].

This study has several limitations. First, it was a single-center retrospective study, and confirmation of the results in a multicenter prospective cohort is needed. Second, the analytic power may have been insufficient to identify certain risk factors associated with outcomes. Finally, the retrospective study design did not allow us to examine GVHD treatment response, symptom burden, and quality of life. Despite these limitations, our results suggested several potential ethnic differences in Japanese patients compared with white patients: a higher proportion of LA GVHD, less frequent gastrointestinal involvement with LA GVHD, a lower incidence of chronic GVHD, more frequent liver involvement with chronic GVHD, a lower risk of NRM after both LA GVHD and chronic GVHD, and a higher risk of discontinued systemic treatment after LA GVHD. A direct comparison between Japanese patients and other ethnicities is needed to formally investigate these ethnic differences. Ethnic differences may be related to differences in minor histocompatibility [30-32], genetic polymorphisms [33], and environmental or dietary variations. In addition, studies showed that intestinal microbiome was associated with the risk of GVHD-related mortality [34], and Japanese are known to have unique intestinal microbiome, possibly due to their dietary characteristics [35].

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