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Survivorship

Resolved versus Active Chronic Graft-versus-Host Disease: Impact on Post-Transplantation Quality of Life

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The aim of this study was to determine whether impaired quality of life (QOL) persisted among patients who experienced resolved chronic graft-versus-host disease (GVHD) after allogeneic hematopoietic cell transplantation (allo-HCT). Eligible participants were patients who were relapse-free for 3 years after allo-HCT who were age ≥16 years at the time of transplantation and age ≥20 years without relapse at the time of the survey. The Medical Outcomes Study's 36-Item Short-Form Survey (SF-36), the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT), and a visual analog scale (VAS) were administered to assess QOL. Physicians evaluated the current status of chronic GVHD at survey using National Institutes of Health (NIH) criteria, and pre-transplantation characteristics and history of GVHD were extracted from the national transplant registry database. Patients without currently active GVHD but with a history of chronic GVHD were categorized as having "resolved GVHD." Of 1250 patients informed of the study, 1216 provided consent and 1130 were included in the final analysis. A total of 745 patients (66%) had currently active chronic GVHD, 149 (13%) had resolved chronic GVHD, and 236 (21%) never had chronic GVHD after allo-HCT. Multivariable analyses showed that compared with patients with resolved or no chronic GVHD, those with active chronic GVHD reported significantly poorer QOL. The QOL scores were similar in patients with resolved chronic GVHD and those without chronic GVHD. Greater between-group differences were observed in SF-36 Physical component and VAS scores in patients age ≥50 years, but the differences were not statistically significant. Our data indicate that only currently active chronic GVHD has a significant impact on physical, mental, and social QOL in allo-HCT survivors, whereas previous chronic GVHD does not impair QOL if it has been resolved.

INTRODUCTION

Improved outcomes of allogeneic hematopoietic cell transplantation (allo-HCT) in recent years have resulted in a growing number of transplantation survivors [1-4], and the

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importance of long-term survivorship care has been recognized. To effectively deliver this care, it is crucial to target it appropriately and to understand the impact of various late effects on quality of life (QOL) [5-10].

Chronic graft-versus-host disease (GVHD) is a major late complication after allo-HCT that leads to late morbidity and mortality [11,12]. Approximately 30% to 70% of allo-HCT recipients develop chronic GVHD [13,14], and multiple studies have shown the negative impact of chronic GVHD on QOL in long-term survivors [15-17]. In a previous nationwide cross-sectional questionnaire study, we evaluated patient-reported QOL according to affected organs, as well as the severity of chronic GVHD assessed by physicians [18,19]. In that study, which included 1140 pairs of patient and physician questionnaires, we found significant effects on physical, mental, and social aspects of QOL in patients with more severe chronic GVHD at the time of the survey [18].

We also found that even when current GVHD symptoms were categorized as mild, they significantly impaired physical QOL relative to symptom absence. However, in this previous study, we assessed the impact of current symptoms of chronic GVHD on QOL in a cross-sectional manner but did not assess the influence of past history of chronic GVHD on QOL. In an analysis from the Bone Marrow Transplant Survivor Study (BMT-SS), health status was surveyed in a cross-sectional manner, and the data indicated that patients who reported active chronic GVHD symptoms during the previous 12 months were significantly more likely to report functional impairment, activity limitation, and pain [20]. More importantly, they showed that patients with a history of chronic GVHD but without currently active GVHD symptoms (ie, resolved GVHD) reported health status outcomes equivalent to those of patients who had never been diagnosed with chronic GVHD.

The aims of the present study were to explore the impact of past history of chronic GVHD on QOL in allo-HCT survivors, and to provide long-term survivorship care teams with useful information on targets of care and needed resources in this population. To investigate this issue, we analyzed data from a nationwide cross-sectional QOL survey and a national transplant registry database.

METHODS

Study Design and Participants

Eligibility criteria for this study included allo-HCT for hematologic disease performed between 1995 and 2009, age 16 years or older at the time of transplantation and 20 years or older at the time of the survey, and relapse-free status at the time of the survey. A total of 3301 eligible patients registered at 47 participating centers were identified in the national transplant registry database [21,22]. Participants were enrolled between December 2012 and September 2014 while visiting a participating center as an outpatient. Of the 1250 patients informed of the study, consent was obtained from 1216 (97%), and 1149 (95% of those who consented) returned the questionnaires. We asked participating patients to complete the questionnaire within 1 month from the date of consent, and instructed physicians to report clinical information on the date of consent or within the previous 3 months. Nine patients were excluded because of a time lag >4 months between the patient and physician questionnaire responses. Consequently, 1140 pairs of patient and physician questionnaires were included in the original database [18]. The median difference between patient and physician questionnaire responses was 2 days (range, 0 to 118 days), and was <1 month in 95% of cases.

The study protocol was approved by the Institutional Review Board of each participating center. All subjects provided informed consent in accordance with the Declaration of Helsinki.

QOL Measures, Chronic GVHD Assessment, and Other Data Sources

The SF-36, the FACT-BMT, and a VAS were administered to assess patient-reported QOL at a single time point. On all these scales, higher scores indicate better QOL.

The SF-36 version 2 is a comprehensive 36-item questionnaire that assesses self-reported health. SF-36 normative scores for the Japanese general population enabled us to compare the scores of allo-HCT recipients with those of the general population. For the SF-36, we used a 3-component model that was validated to have a better fit for Asian populations [23,24] and that provided a role/social component summary score (RCS) in addition to physical (PCS) and mental (MCS) component summary scores.

The FACT-BMT version 4.0 is a disease-specific scale that consists of a 37-item self-reported questionnaire including the 27-item FACT-General (FACT-G) and a 10-item subscale assessing concerns related to transplantation (BMTS) [25]. The FACT-G has 4 QOL domains: physical, social/family, emotional, and functional well-being (0-108). The FACT-BMT Trial Outcome Index (TOI), the sum of physical and functional well-being and BMTS scores (0 to 96), provides an efficient summary index of physical/functional outcomes. The FACT-BMT total score is the sum of the FACT-G and BMTS (0 to 148) scores.

The VAS is used to rate health on a scale with endpoints labeled "best imaginable health state" at the top and "worst imaginable health state" at the bottom, with corresponding numeric values of 100 and 0.

Participating primary physicians graded the overall and organ-specific severity of their patients' chronic GVHD at the time of the survey based on NIH criteria [26]. Considering that chronic GVHD is a dynamic syndrome, we asked participating physicians to provide clinical information including GVHD status on the date of consent or within the previous 3 months. In addition, the presence or absence of a previous history of acute or chronic GVHD was extracted from the national transplant registry database [22]; this information had been prospectively reported by healthcare professionals from each institution. Pretransplantation characteristics, including disease type, sex, age at HCT, date of HCT, donor type, preparative regimen, GVHD prophylaxis, performance status (PS) at HCT, and number of HCTs, were also extracted from the registry database.

Statistical Analysis

Standard algorithms were used to compute scores for SF-36 [23,24] and FACT-BMT [25]. Multivariable models were constructed to examine the relationship between QOL scores and employment status after controlling for background covariates, including age at survey (by decade), sex, disease (acute myelogenous leukemia/myelodysplastic syndrome/myeloproliferative disease/chronic myelogenous leukemia, lymphoid leukemia, lymphoma, myeloma, or nonmalignant disease), time from allo-HCT (<5, 5 to 6, 7 to 9, or ≥10 years), donor type (related bone marrow [BM], related peripheral blood [PB], HLA well-matched unrelated BM, HLA-mismatched unrelated BM, or unrelated cord blood [CB]), preparative regimen (myeloablative or other), GVHD prophylaxis (cyclosporine-based or tacrolimus-based), PS at HCT, and number of HCTs (1 or ≥2). Adjusted mean SF-36 summary scores were obtained as norm-based scores (mean, 50 ± 10 based on the Japanese general population; n = 2279) after adjusting for the same covariates. We considered a *P*value <.01 to be statistically significant. A minimum clinically important difference (MCID) in QOL scores was defined as .5 SD [27], as in our previous report [18]. Data were analyzed with SPSS version 22.0 (IBM, Armonk, NY) and SAS/STAT version 9.2 (SAS Institute, Cary, NC). (For original data, please contact skurosaw@ncc.go.jp.)

RESULTS

Characteristics of the Patient Cohort

Of the 1140 participants in this study, valid data on the past history of acute or chronic GVHD were available for 1130 patients in the national transplant registry database, and these patients were included in this analysis. Their baseline demographic, disease, and transplantation characteristics are presented in Table 1. The median age at transplantation was 43 years (range, 16 to 68 years), and the median age at the time of the survey was 51 years (range, 20 to 77 years). Males accounted for 52% of the analyzed population. The median time after allo-HCT was 7.1 years (range, 3.3 to 18.9 years). Donor type was related BM in 22% of patients, related PB in 21%, unrelated BM in 40%, and unrelated CB in 17%.

Status of Chronic GVHD

Of the 1130 study participants, 745 (66%) had physician-reported currently active chronic GVHD (ie, active GVHD) at the time of the survey. By NIH global severity score, chronic GVHD symptoms were mild in 342 patients, moderate in 297, and severe in 106. In the 385 participants without chronic GVHD symptoms at the time of the survey, 149 (13%) had a past history of chronic GVHD (ie, resolved GVHD), and 236 (21%) never had chronic GVHD symptoms after allo-HCT

Table 1
Characteristics of the Study Participants According to Chronic GVHD Status

Table1. Characteristics of the study participants according to cGVHD status									
	Total	No cGVHD	Resolved cGVHD	Active cGVHD	*P value*		
	(n = 1,130)	(n = 236)	(n = 149)	(n = 745)	*no vs resolved*	*no vs active*	*resolved vs active*
Characteristics	n (%)	n (%)	n (%)	n (%)			
Age at transplant					*0.696*	*0.001*	*0.021*
–19	51 (5)	14 (6)	9 (6)	28 (4)			
20–29	147 (13)	45 (19)	25 (17)	77 (10)			
30–39	265 (23)	59 (25)	34 (23)	172 (23)			
40–49	297 (26)	53 (22)	42 (28)	202 (27)			
50–59	296 (26)	55 (23)	36 (24)	205 (28)			
60–	74 (7)	10 (4)	3 (2)	61 (8)			
Age at survey					*0.783*	*0.008*	*0.100*
20–29	66 (6)	21 (9)	9 (6)	36 (5)			
30–39	156 (14)	41 (17)	24 (16)	91 (12)			
40–49	286 (25)	62 (26)	46 (31)	178 (24)			
50–59	301 (27)	57 (24)	36 (24)	208 (28)			
60–	321 (28)	55 (23)	34 (23)	232 (31)			
Gender					*0.165*	*0.516*	*0.281*
Male	584 (52)	128 (54)	70 (47)	386 (52)			
Female	546 (48)	108 (46)	79 (53)	359 (48)			
Years after transplantation					*0.041*	*0.114*	*0.008*
<5	262 (23)	49 (21)	22 (15)	191 (26)			
5–6	280 (25)	68 (29)	31 (21)	181 (24)			
7–9	276 (24)	48 (20)	45 (30)	183 (25)			
10 or longer	312 (28)	71 (30)	51 (34)	190 (26)			
Background disease					*0.046*	*0.239*	*0.077*
AML/MDS/MPD/CML	682 (60)	134 (57)	94 (63)	454 (61)			
ALL/Other leukemia	190 (17)	43 (18)	32 (21)	115 (15)			
NHL/HL/ATL/Other lymphoma	197 (17)	39 (17)	21 (14)	137 (18)			
MM/PCD	12 (1)	3 (1)	0 (0)	9 (1)			
AA/PNH	49 (4)	17 (7)	2 (1)	30 (4)			
Donor					*0.819*	*0.000*	*0.009*
Related BM	244 (22)	64 (27)	42 (28)	138 (19)			
Related PB	234 (21)	32 (14)	26 (17)	176 (24)			
Unrelated BM	454 (40)	105 (44)	61 (41)	288 (39)			
HLA well matched	265 (23)	67 (28)	41 (28)	157 (21)			
HLA mismatched	189 (17)	38 (16)	20 (13)	131 (18)			
UCB	197 (17)	35 (15)	20 (13)	142 (19)			
Preparative regimen					*0.551*	*0.015*	*0.007*
Myeloablative	630 (56)	142 (60)	94 (63)	394 (53)			
Others	390 (35)	68 (29)	39 (26)	283 (38)			
Data not available	110 (10)	26 (11)	16 (11)	68 (9)			
GVHD prophylaxis					*0.156*	*0.238*	*0.505*
Cyclosporine-based	566 (50)	111 (47)	81 (54)	374 (50)			
Tacrolimus-based	532 (47)	122 (52)	66 (44)	344 (46)			
Data not available	32 (3)	3 (1)	2 (1)	27 (4)			
Performance status at transplant					*0.461*	*0.382*	*0.890*
0	633 (56)	140 (59)	78 (52)	415 (56)			
1	307 (27)	54 (23)	40 (27)	213 (29)			
2	29 (3)	4 (2)	4 (3)	21 (3)			
3 or 4	9 (1)	3 (1)	0 (0)	6 (1)			
Data not available	152 (13)	35 (15)	27 (18)	90 (12)			
Transplant number					*0.090*	*0.710*	*0.035*
1	1034 (92)	216 (92)	143 (96)	675 (91)			
2–	95 (8)	20 (8)	6 (4)	69 (9)			
Data not available	1 (0)	0 (0)	0 (0)	1 (0)			
Immunosuppressant therapy					*0.952*	*0.000*	*0.000*
No	897 (79)	233 (99)	147 (99)	517 (69)			
Yes	233 (21)	3 (1)	2 (1)	228 (31)			
Acute GVHD					*0.000*	*0.000*	*0.238*
No	449 (40)	123 (52)	48 (32)	278 (37)			
Yes	682 (60)	113 (48)	101 (68)	468 (63)			

cGVHD indicates chronic graft-versus-host disease

(ie, no GVHD). Among these 3 groups defined by chronic GVHD status (Table 1), the active GVHD group had higher proportions of patients of older age (at both HCT and the survey), receipt of allo-HCT from related PB donors, and use of preparative regimens other than myeloablative regimens. The resolved GVHD group had a higher proportion of participants who survived for ≥7 years after HCT. At the time of the survey, 233 participants were taking immunosuppressant drugs, and this was significantly more likely in the active GVHD group (31%, versus 1% in the no GVHD and resolved GVHD groups). The no GVHD group had a significantly lower proportion of participants with a past history of acute GVHD.

QOL According to Chronic GVHD Status

Figure 1 shows the adjusted mean QOL scores in the 3 groups according to chronic GVHD status: no GVHD, resolved GVHD, and active GVHD. In most of the QOL domains, the no GVHD group demonstrated the highest scores, and in that group, adjusted mean scores on the SF-36 PCS, MCS, and RCS were comparable to or higher than those of the general population. The QOL scores in the resolved GVHD group were comparable overall to those in the no GVHD group, and there were no significant differences in QOL score in any domains between these 2 groups (Figure 1, Table 2). The active GVHD group had the lowest QOL scores in all domains. The differences in scores between the active GVHD group and no GVHD group were statistically significant in all domains ($P < .001$), and differences in all domains other than MCS and RCS reached MCID. The differences in scores between the active GVHD and resolved GVHD groups were statistically significant in all domains ($P < .001$) other than MCS, and differences in PCS, TOI, and FACT-BMT total reached MCID. These results did not change when the history of acute GVHD was added in multivariable analyses.

QOL According to Chronic GVHD Status and Age

Figure 2 and Table 3 show the adjusted mean QOL scores and their differences according to chronic GVHD status separately in younger versus older patients (age at survey <50 years and ≥50 years, respectively). In both age cohorts, the no GVHD group had the highest overall QOL scores in all domains, including PCS, MCS, and RCS.

In patients age <50 years, the active GVHD group had the lowest QOL scores in all the domains, accompanied by statistically significant differences and MCID compared with the no GVHD and resolved GVHD groups in PCS, TOI, FACT-BMT total, and VAS. On the other hand, as with the results from the overall patient sample, QOL scores in the resolved GVHD group were comparable to those in the no GVHD group in all QOL domains.

In patients age ≥50 years, the active GVHD group had statistically significantly lower QOL scores compared with the no GVHD group in all domains other than MCS, and most of them reached MCID. Compared with the younger patients, who showed similar QOL scores in the resolved GVHD and no GVHD groups, the resolved GVHD group in the older age group had lower QOL scores compared with the no GVHD group, especially in PCS and VAS; the difference in PCS scores was 3.8 points ($P = .080$), and that in VAS scores was 5.5 points ($P = .134$). Similarly, the largest differences in QOL scores between the younger and older patients were seen in PCS and VAS in the resolved GVHD group (5.9 and 5.5 points higher, respectively, in the younger patients), and these differences in QOL scores according to patient age were smaller in the active GVHD group.

DISCUSSION

Chronic GVHD is a major complication after allo-HCT that leads to late morbidity and mortality, and multiple studies have reported a significant negative impact of chronic GVHD on QOL in long-term survivors [6,15-18]. In our previous report, which analyzed 1140 pairs of patient-reported outcomes and physician-assessed GVHD severity and sites, we showed that even mild chronic GVHD symptoms significantly diminished patients' QOL [18]. In the present analysis, we abstracted information from a nationwide transplant registry database on the presence or absence of chronic GVHD that existed before the start of the survey, and separately evaluated QOL in patients who had never been diagnosed with chronic GVHD and those who had a history of chronic GVHD. Multivariable analyses that adjusted for background covariates showed that physical, mental, and social QOL were equivalent in patients with resolved GVHD and those who had never been diagnosed with chronic GVHD.

The BMT-SS conducted a cross-sectional study to assess the impact of chronic GVHD on overall health status in 584 HCT survivors [20]. In that study, participants completed the

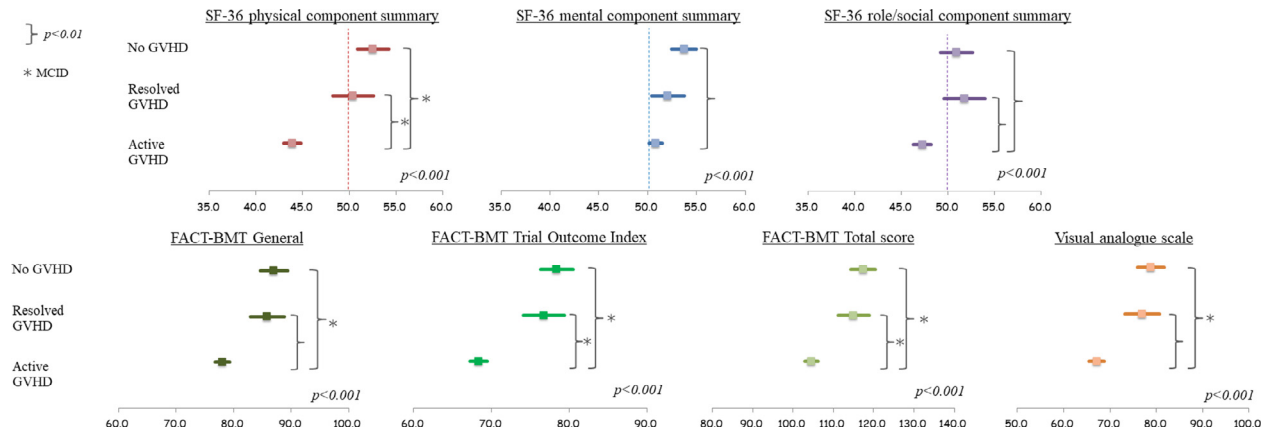

Figure 1. Adjusted mean SF-36 summary scores, FACT-BMT General, TOI, and total scores, and VAS scores by chronic GVHD status. QOL scores adjusted for background covariates are presented according to the 3 chronic GVHD status groups: no GVHD, n = 236; resolved GVHD, n = 149; and active GVHD, n = 745. The mean SF-36 summary score of 50 in the general population is indicated by the vertical dotted lines. MCID are indicated by asterisks.

Table 2
Multivariable Models Examining QOL by Chronic GVHD Status

	Resolved GVHD vs no GVHD					Active GVHD vs no GVHD					Active GVHD vs resolved GVHD				
	Estimate	95%CI			*P*	Estimate	95%CI			*P*	Estimate	95%CI			*P*
SF-36															
Physical component summary	-2.09	(-4.81	–	0.64)	*0.133*	*-8.61	(-10.53	–	-6.68)	*0.000*	*-6.52	(-8.88	–	-4.16)	*0.000*
Mental component summary	-1.63	(-3.70	–	0.44)	*0.123*	-2.83	(-4.30	–	-1.37)	*0.000*	-1.21	(-3.00	–	0.59)	*0.187*
Role/Social component summary	0.88	(-1.89	–	3.65)	*0.532*	-3.64	(-5.60	–	-1.69)	*0.000*	-4.52	(-6.92	–	-2.13)	*0.000*
FACT-BMT															
FACT trial outcome index	-1.68	(-5.05	–	1.68)	*0.326*	*-10.02	(-12.41	–	-7.62)	*0.000*	*-8.33	(-11.23	–	-5.43)	*0.000*
FACT-G total	-1.13	(-4.90	–	2.64)	*0.556*	*-8.80	(-11.49	–	-6.12)	*0.000*	-7.67	(-10.92	–	-4.43)	*0.000*
FACT-BMT total	-2.32	(-7.19	–	2.56)	*0.351*	*-12.79	(-16.27	–	-9.31)	*0.000*	*-10.47	(-14.66	–	-6.28)	*0.000*
VAS															
Patient	-1.83	(-6.58	–	2.92)	*0.450*	*-11.53	(-14.84	–	-8.22)	*0.000*	-9.70	(-13.82	–	-5.58)	*0.000*

QOL indicates quality of life; GVHD, graft-versus-host disease; SF-36, the MOS 36-Item Short-Form Health Survey; FACT-BMT, Functional Assessment of Cancer Therapy-BMT; VAS, visual analogue scale.
The estimate represents the difference in QOL scores between the two groups. A negative difference indicates that the group on the left has a lower QOL score (inferior QOL).
*The differences reached clinical significance.

BMT-SS questionnaire, which was developed to address topics related to HCT survivor population, and 6 health status domains, including general health, mental health, functional impairment, activity limitation, pain, and fear/anxiety were assessed. The diagnosis of chronic GVHD was abstracted from a prospectively collected database, whereas the activity of chronic GVHD was self-reported by patients using a questionnaire. The researchers evaluated the prevalence of adverse health outcomes with regard to chronic GVHD status and found that patients with active chronic GVHD had a significantly higher risk of adverse health outcomes, and that the prevalence of these outcomes did not differ between patients with no GVHD and those with resolved GVHD. In the BMT-SS, the year of transplantation ranged from 1975 to 2000 and the current status of chronic GVHD was self-reported, but its results and our present findings both demonstrate that only the current status of chronic GVHD had a major impact on patients' QOL and physical, mental, and social functioning and QOL. In our study, patient history and the current status of chronic GVHD were both assessed by physicians. In addition, we found differences in patient-reported QOL assessed using 3 validated QOL tools in 3 groups with varied chronic GVHD status, as well as in comparison with the general population, and we also evaluated the clinical importance of these differences.

Several studies have demonstrated a relationship between patient age and QOL [5,15], but whether older age necessarily leads to worse QOL remains controversial. To define the specific needs and targets of care in different age groups, we evaluated the association between chronic GVHD status and QOL separately in younger and older age groups. Although not statistically significant, there were larger differences in PCS and VAS between the no GVHD group and the resolved GVHD group in patients age $\geq$50 years at the time of the survey. In addition, in the resolved GVHD group, there were larger differences in PCS and VAS scores between the younger and older patients, possibly indicating that in older patients with a prior history of chronic GVHD, impaired QOL tends to persist, especially in areas rated by the PCS and VAS. In our previous analysis, we reported that the VAS was strongly correlated with general health perceptions, vitality, and physical well-being [18]. Interestingly, in the present study, the differences in scores between the younger and older age groups were larger in the resolved GVHD group than in the active GVHD group.

Several limitations of this study should be discussed. First, because this was a cross-sectional survey, the presence or absence of current chronic GVHD and QOL were assessed at various time points after allo-HCT. Our cohort was composed of 1140 long-term survivors with a median follow-up of 7 years after allo-HCT, and the shortest interval after allo-HCT was 3 years. Considering the fact that multiple reports have shown that QOL recovers to baseline by 1 to 2 years after allo-HCT, and that we used multivariable models to adjust for the time after HCT [17,28-30], we feel that the range of time points across which the information was collected should not have markedly affected the results. Second, because the date of remission of past chronic GVHD was not available in the registry database, this analysis did not include the time from past GVHD resolution to current survey date for patients with resolved GVHD, or the duration of chronic GVHD for those with active chronic GVHD at the time of the survey. We acknowledge that these time factors may have crucial impacts on QOL, and as such warrant investigation in future prospective studies. Other variables that we did not obtain from the

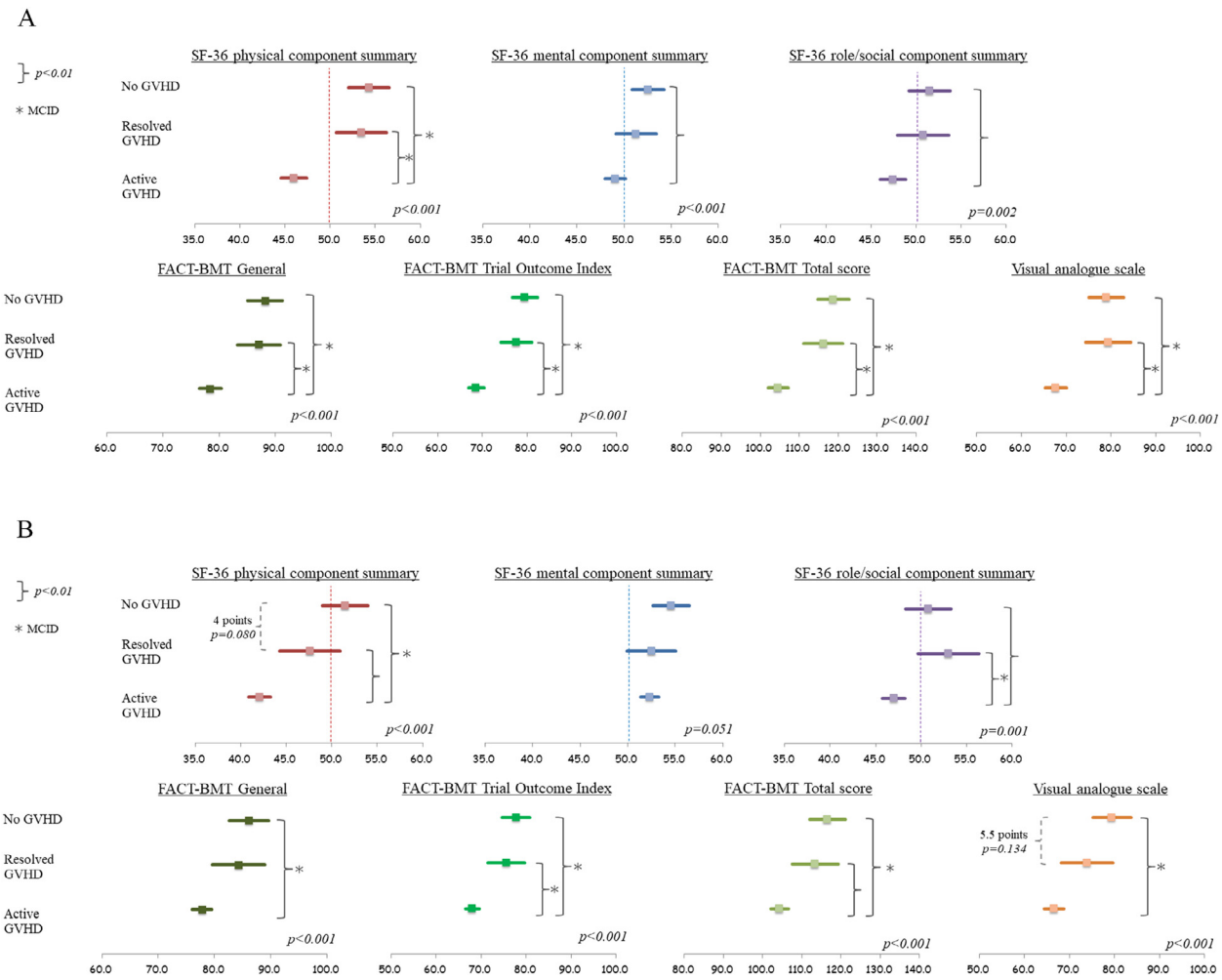

Figure 2. QOL scores by chronic GVHD status; subgroup analysis by patient age at survey: <50 years (A) and ≥50 years (B). QOL scores adjusted for background covariates are presented according to the 3 chronic GVHD status groups separately for younger and older patients. The mean SF-36 summary score of 50 in the general population is indicated by the vertical dotted lines. MCID is indicated by asterisks.

registry database were sequelae after chronic GVHD and other complications that may have affected QOL. Finally, of the 3301 patients identified in the registry database, only 1250 were informed of the study. All the participating centers had an enrollment period of at least 6 months, but it is still possible that patients who had to be seen at shorter intervals were more likely to be included. However, considering the strikingly high consent (97%) and return (95%) rates, we believe that any bias due to patient preference or judgment was rather small.

In conclusion, our findings show that the negative impact of a past history of chronic GVHD was minimal when the condition was successfully treated, and that patients with resolved GVHD had comparable QOL to survivors who had never been diagnosed with chronic GVHD. Results from subgroup analyses suggest that older patients might experience the negative impact of chronic GVHD even after the resolution of symptoms. The influence of past chronic GVHD on QOL has not previously been surveyed by validated QOL questionnaires; other strengths of this study include the large number of long-term HCT survivors who participated and the diagnosis of chronic GVHD by physicians. Identifying high-risk populations may allow multidisciplinary health care professionals to carry out more focused and efficient monitoring and interventions in long-term survivorship care.

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Authorship statement: S.K., K.O., and Y.A. designed the study, manipulated the data file, and interpreted the data as the primary investigators of this study. S.K. performed data analysis and wrote the manuscript. T. Yamaguchi was primarily responsible for data analysis and interpretation of the data. A.Y. prepared the data file and interpreted data. T.F., H.K., T.M., S.T., T.K., M.I., K.M., Y.U., and T.T. gathered patient data and interpreted data. S.T., T. Yamashita, Y.I., Y.K., and S.O. helped design the study, interpreted data, and provided administrative support for the study.

Table 3
Multivariable Models Examining QOL by Chronic GVHD Status and Age at Survey

	Resolved GVHD vs no GVHD				Active GVHD vs no GVHD				Active GVHD vs resolved GVHD			
	Estimate	95%CI		*P*	Estimate	95%CI		*P*	Estimate	95%CI		*P*
Age at survey: under 50												
SF-36												
Physical component summary	-0.82	(-4.40	– 2.75)	*0.651*	*-8.30	(-10.94	– -5.65)	*0.000*	*-7.47	(-10.62	– -4.33)	*0.000*
Mental component summary	-1.28	(-4.01	– 1.46)	*0.359*	-3.44	(-5.46	– -1.42)	*0.001*	-2.16	(-4.56	– 0.24)	*0.077*
Role/Social component summary	-0.75	(-4.39	– 2.89)	*0.686*	-4.08	(-6.77	– -1.39)	*0.003*	-3.33	(-6.52	– -0.14)	*0.041*
FACT-BMT												
FACT trial outcome index	-1.91	(-6.34	– 2.51)	*0.396*	*-10.91	(-14.19	– -7.62)	*0.000*	*-9.00	(-12.87	– -5.12)	*0.000*
FACT-G total	-1.11	(-6.03	– 3.82)	*0.658*	*-9.74	(-13.40	– -6.08)	*0.000*	*-8.63	(-12.94	– -4.32)	*0.000*
FACT-BMT total	-2.57	(-9.00	– 3.85)	*0.431*	*-14.12	(-18.90	– -9.34)	*0.000*	*-11.54	(-17.16	– -5.93)	*0.000*
VAS												
Patient	0.40	(-5.94	– 6.75)	*0.900*	*-11.26	(-15.86	– -6.66)	*0.000*	*-11.66	(-17.24	– -6.09)	*0.000*
Age at survey: 50 or over												
SF-36												
Physical component summary	-3.75	(-7.95	– 0.45)	*0.080*	*-9.39	(-12.21	– -6.58)	*0.000*	-5.64	(-9.23	– -2.05)	*0.002*
Mental component summary	-2.03	(-5.23	– 1.17)	*0.212*	-2.17	(-4.31	– -0.02)	*0.048*	-0.13	(-2.87	– 2.60)	*0.924*
Role/Social component summary	2.22	(-1.98	– 6.43)	*0.300*	-3.74	(-6.56	– -0.92)	*0.010*	*-5.96	(-9.56	– -2.36)	*0.001*
FACT-BMT												
FACT trial outcome index	-2.17	(-7.35	– 3.01)	*0.410*	*-9.70	(-13.21	– -6.19)	*0.000*	*-7.53	(-11.94	– -3.12)	*0.001*
FACT-G total	-1.85	(-7.68	– 3.98)	*0.534*	*-8.24	(-12.19	– -4.29)	*0.000*	-6.39	(-11.35	– -1.43)	*0.012*
FACT-BMT total	-3.01	(-10.51	– 4.48)	*0.430*	*-12.05	(-17.16	– -6.95)	*0.000*	-9.04	(-15.39	– -2.69)	*0.005*
VAS												
Patient	-5.46	(-12.62	– 1.70)	*0.134*	*-12.60	(-17.39	– -7.81)	*0.000*	-7.14	(-13.29	– -0.99)	*0.023*

QOL indicates quality of life; GVHD, graft-versus-host disease; SF-36, the MOS 36-Item Short-Form Health Survey; FACT-BMT, Functional Assessment of Cancer Therapy-BMT; VAS, visual analogue scale.

The estimate represents the difference in QOL scores between the two groups. A negative difference indicates that the group on the left has a lower QOL score (inferior QOL).

*The differences reached clinical significance.

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