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ORIGINAL ARTICLE

Late complications and quality of life assessment for survivors receiving allogeneic hematopoietic stem cell transplantation

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Abstract

Purpose The survival rates of patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) have improved. However, HSCT can induce significant long-term complications. Therefore, we investigated the late complications and risk factors for quality of life (QOL) post-HSCT.

Methods We retrospectively analyzed 67 adult survivors over 2 years after HSCT between 2015 and 2018 at Ulsan University Hospital, Ulsan, Korea. The survey data including FACT-BMT, Hospital Anxiety and Depression Scale, and NCCN Distress Thermometer were collected as patient-reported outcomes using a tablet PC during a routine practice of survivorship clinic.

Results The median age was 46 years. The most common symptom was fatigue (80.6%). Younger age (< 60 years), acute lymphoblastic leukemia (ALL), chronic graft-versus-host disease (GVHD), and immunosuppressant use were significantly associated with worse QOL and depression. Additionally, younger survivors (< 60 years) showed significantly more fatigue and anxiety compared with elderly survivors (≥ 60 years). Female sex was significantly associated with lower physical well-being and higher distress than male sex.

Conclusion Younger patients (< 60 years), female, ALL, chronic GVHD, and continuous immunosuppressant use were significant risk factors for worse QOL and depression. Hence, creating a more active survivorship care plan after HSCT, specifically for these patients, is required.

Keywords Allogeneic hematopoietic cell transplantation · Late complications · Quality of life · FACT-BMT · Fatigue · Hospital Anxiety and Depression Scale

Abbreviations

HSCT	Allogeneic hematopoietic stem cell transplantation
GVHD	Graft-versus-host disease
QOL	Quality of life
FACT-BMT	Functional Assessment of Cancer Therapy-Bone Marrow Transplantation
BMTS	Bone Marrow Transplantation Subscale
PWB	Physical well-being
SFWB	Social/family well-being
EWB	Emotional well-being
FWB	Functional well-being
HADS	Hospital Anxiety and Depression Scale
HADS-A	HADS-anxiety
HADS-D	HADS-depression
NCCN DT	National Comprehensive Cancer Network's Distress Thermometer
BPI	Brief Pain Inventory
AML	Acute myeloid leukemia
ALL	Acute lymphoblastic leukemia
AA	Aplastic anemia
MDS	Myelodysplastic syndrome
RIC	Reduced intensity conditioning

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MAC	Myeloablative conditioning
ATG	Anti-thymocyte globulin
TOI	Total Outcome Index

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is the most effective therapy for most hematological malignancies [1]. The long-term survival probability for HSCT recipients continues to improve with several advancements in transplantation techniques and supportive care practices [2, 3]. However, most patients with hematologic malignancies should receive several cycles of intensive chemotherapies before undergoing HSCT to reduce relapse risks. Moreover, chemotherapy agents used especially in HSCT compared with other solid cancers are even more toxic, since conditioning regimens in HSCT are often administered at myeloablative doses within a short period of 1 week [4]. HSCT is physically and psychosocially demanding and can cause various late complications, including chronic graft-versus-host disease (GVHD), infection, cardiovascular, pulmonary, renal, neurological toxicity, endocrine dysfunction and secondary cancers, quality of life (QOL) impairment, psychosocial issues, sexual and fertility concerns, and financial toxicity [4–6]. Compared with autologous stem cell transplantation, HSCT can have a higher risk of transplantation-related mortality and lead to more late complications, because acute and chronic GVHD can be caused only in HSCT. HSCT survivors are at a higher risk of long-term mortality post-HSCT throughout life after HSCT, with a four- to ninefold greater mortality risk, compared with age-adjusted population norms [2–4]. Therefore, long-term survivorship care is more important in HSCT survivors than any other cancer survivors. Although there have been several reports for the late effects of HSCT [7–14], survivorship studies have been mostly conducted in children and young adults, and QOL data for adult patients undergoing HSCT is insufficient. Moreover, several aspects of survivorship care after HSCT remain elusive; hence, much further effort is required to understand, monitor, and integrate the management into routine survivorship care. Therefore, we aimed to investigate the unmet needs for late complications and risk factors affecting the QOL, fatigue, anxiety, depression, and distress for adult HSCT survivors.

Methods

We retrospectively analyzed 67 adult survivors without relapse over 2 years after undergoing HSCT between 2006 and 2017 at the Ulsan University Hospital, Korea. Patients who did not have survey data, had a relapse, or died from any cause within 2 years after HSCT were excluded.

Table 1 Baseline clinical characteristics ($n = 67$)

Clinical factors	No. (%)
Age, median (range), years	45 (21–70)
Sex, M/F	38/29 (56.7/43.3)
Diagnosis	
Acute myeloid leukemia	28 (41.8)
Acute lymphoblastic leukemia	15 (22.4)
Myelodysplastic syndrome	7 (10.4)
Aplastic anemia	12 (17.9)
Chronic myeloid leukemia	2 (3.0)
Lymphoma	2 (3.0)
Blastic plasmacytoid dendritic cell neoplasm	1 (1.5)
Donor	
Matched sibling	16 (23.9)
Unrelated	41 (61.2)
Haploidentical family	10 (14.9)
Conditioning intensity	
MAC	17 (25.3)
RIC	50 (74.7)
Conditioning regimen	
BuCy	13 (19.4)
BuFlu	36 (53.8)
Others[a]	17 (25.4)
ATG	
Yes/no	51 (76.1)/16 (23.1)
Acute GVHD	22 (32.8)
Grades 2–4	15 (22.4)
Chronic GVHD	36 (53.7)
Continuous immunosuppressant use	19 (28.4)

MAC, myeloablative conditioning; *RIC*, reduced intensity conditioning; *BuCy*, busulfan plus cyclophosphamide; *BuFlu*, busulfan plus fludarabine; *GVHD*, graft-versus-host disease; *ATG*, anti-thymocyte globulin

[a] Other regimens include fludarabine plus melphalan, cyclophosphamide plus melphalan, cyclophosphamide plus fludarabine, and cyclophosphamide or fludarabine

Patients who underwent autologous HSCT were also excluded. The survivorship surveys as patient-reported outcomes had been performed using a tablet PC as a routine practice to evaluate patients' medical status at the survivorship clinic of Ulsan University Hospital, Korea, since 2015 and collected as the electronic medical records. We analyzed the survivorship survey data collected between 2015 and 2018 with a retrospective chart review. Written informed consent by the patients was waived due to the retrospective nature of our study. The median time of the survey was 25.7 months after HSCT. The survey questionnaire consisted of physical and psychological symptoms, socioeconomic status, QOL, lifestyle, and regular health screening tests. Data for baseline clinicopathological features, treatments, and outcomes were collected from

Table 2 Symptoms and quality of life assessment for late complications in hematopoietic stem cell transplantation survivors

	No. (%)
Pain	16 (23.9)
Headache	9 (13.4)
Chest pain	10 (14.9)
Shoulder pain	5 (7.5)
Knee pain	5 (7.5)
Back pain	2 (3.0)
Wrist pain	3 (4.5)
Ankle pain	3 (4.5)
Other pain	5 (7.5)
NRS pain scale(0–10), median (range)	3 (1–9)
Fatigue	54 (80.6)
Brief fatigue inventory (0–10)	3 (0–10)
Dizziness	10 (14.9)
Ocular	
Dryness	25 (37.3)
Conjunctival injection	22 (32.8)
Oral	
Dryness	15 (22.4)
Gingivitis/dental caries	16 (23.9)
Oral pain	23 (34.3)
Respiratory	
Cough/sputum	18 (26.9)
Cardiac and vascular	
Chest pain	10 (14.9)
Gastrointestinal	
Dyspepsia	13 (19.4)
Constipation	6 (9.0)
Diarrhea	5 (7.5)
Hematochezia	3 (4.5)
Renal and genitourinary	
Dysuria/hematuria	3 (4.5)/2 (3.0)
Abnormal vaginal bleeding	1 (1.5)
Muscle and connective tissue	
Joint stiffness/pain	14 (20.9)
Skin	
Rash or pruritus	13 (19.4)
Nervous system	
Insomnia	23 (34.3)
Memory disturbance	20 (29.9)
Weight	
Gain/loss	27 (40.3)/6 (9.0)
Weight change	
1–2 kg	10 (14.9)
3–4 kg	18 (26.9)
≥ 5 kg	5 (7.5)
Psychological	
Anxiety (HADS-A) (≥ 8)	10 (14.9)
Depression (HADS-D) (≥ 8)	9 (13.6)
NCCN Distress Thermometer (0–10) (≥ 4)	7 (10.4)

Table 2 (continued)

	No. (%)
Quality of life assessment, FACT-BMT (version 4.0) ($n = 56$), mean (SD)	
PWB	24.9 (3.76)
SWB	18.3 (5.59)
EWB	19.6 (3.64)
FWB	20.6 (6.38)
FACT-G	83.3 (13.59)
BMTS	29.2 (6.21)
Total	112.5 (18.67)
TOI	74.6 (14.10)

HSCT, allogeneic hematopoietic stem cell transplantation; *PWB*, physical well-being; *SWB*, social/family well-being; *EWB*, emotional well-being; *FWB*, functional well-being; *FACT-G*, Functional Assessment of Cancer Therapy-General; *BMTS*, Bone Marrow Transplantation Subscale; *TOI*, Trial Outcome Index

the medical records of each patient. The Institutional Review Boards of Ulsan University Hospital, Korea (UUH 2018-12-004-002), approved this study.

The Functional Assessment of cancer Therapy-Bone Marrow Transplantation

The QOL measurement using the Functional Assessment of Cancer Therapy-Bone Marrow Transplantation (FACT-BMT), Korean version 4.0 [15, 16], was obtained in 56 patients. The FACT-BMT is the Bone Marrow Transplantation Subscale (BMTS) added to the FACT-G that consisted of 27 items including four QOL categories (physical well-being [PWB], social/family well-being [SFWB], emotional well-being [EWB], and functional well-being [FWB]) [16]. The BMTS includes 23 items to evaluate QOL of HSCT survivors [15].

The Hospital Anxiety and Depression Scale

To screen for anxiety and depression, the Hospital Anxiety and Depression Scale (HADS), Korean version [17, 18], was included in the survey. The HADS consists of a 14-item, self-report measure for anxiety (7 items) (HADS-A) and depression (7 items) (HADS-D). For each item, respondents choose one of four options from 0 to 3, and the sum of scores for each item ranges from 0 (no anxiety and no depression) to 42 (extreme anxiety and depression) [17]. The cut-off value for screening anxiety and depression was defined as HADS score ≥ 8 for HADS-A and HADS-D, respectively [18].

The National Comprehensive Cancer Network's Distress Thermometer

Distress was assessed using the National Comprehensive Cancer Network's Distress Thermometer (NCCN DT) [19]. The NCCN DT is a visual analog tool that assesses distress levels to respondents in the past week on a scale of 0 (no distress) to 10 (extreme distress). The respondents indicated a yes or no for the NCCN DT in 34 questionnaires on practical, familial, emotional, spiritual/religious, and physical problems. We defined DT score ≥ 4 as clinical meaningful distress [19].

Brief Pain Inventory and fatigue

The Brief Pain Inventory (BPI) can measure pain intensity. The BPI uses the numeric rating scales from 0 (no pain) to 10 (pain as bad as you can imagine) [20]. Fatigue was measured on numeric scales from 0 (no fatigue) to 10 (fatigue as bad as you can imagine) [21].

Statistical analysis

To evaluate differences regarding physical and psychosocial needs, the referring questionnaires were analyzed according to the manufacturer's instructions. Continuous variables were compared using the Mann-Whitney *U* test and one-way ANOVA test. Statistical analyses were performed using the Statistical Package for the Social Sciences version 21.0 software (IBM Statistics, Chicago, IL, USA). For all analyses, two-sided $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Table 1 presents the patient and clinical characteristics; the median age was 45 years (range, 21–70). Acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), aplastic anemia (AA), and myelodysplastic syndrome (MDS) were

Table 3 Quality of life assessment by the Functional Assessment of Cancer Therapy-Bone Marrow Transplantation scale (version 4.0) according to clinical factors

	PWB, mean (SD)	SWB, mean (SD)	EWB, mean (SD)	FWB, mean (SD)	FACT-G, mean (SD)	BMTS, mean (SD)	Total, mean (SD)	TOI, mean (SD)
Age, years	*P = 0.002**	*P = 0.788*	*P = 0.006**	*P = 0.014**	*P = 0.005**	*P = 0.021**	*P = 0.001**	*P = 0.002**
< 60	24.3 (3.96)	18.9 (3.59)	18.5 (5.37)	19.7 (6.61)	81.4 (14.25)	28.3 (6.41)	109.7 (19.84)	72.3 (14.62)
≥ 60	26.9 (1.83)	21.9 (2.84)	17.9 (6.6)	23.8 (4.26)	90.6 (7.58)	32.3 (4.35)	7122.8 (7.52)	83.0 (7.86)
Sex	*P = 0.046**	P = 0.128	P = 0.535	P = 0.315	P = 0.239	*P = 0.036**	P = 0.125	P = 0.054
M	25.8 (3.07)	20.2 (3.46)	17.9 (6.19)	21.3 (7.19)	85.3 (13.29)	30.7 (6.37)	116.0 (17.95)	77.8 (14.44)
F	23.7 (4.25)	18.7 (3.74)	18.8 (4.79)	19.6 (5.20)	80.9 (13.84)	27.3 (5.57)	108.2 (19.00)	70.6 (12.86)
Diagnosis	P = 0.075	*P = 0.004**	P = 0.562	*P = 0.002**	*P = 0.002**	*P = 0.029**	*P = 0.003**	*P = 0.006**
AML, MDS, CML, AA, and lymphoma	25.4 (3.31)	20.2 (3.45)	18.5 (6.03)	21.8 (6.23)	85.9 (13.13)	30.1 (6.10)	115.9 (17.9)	77.2 (13.38)
ALL	22.5 (4.67)	16.7 (3.06)	17.7 (3.29)	15.8 (4.70)	72.8 (10.24)	25.5 (5.52)	98.3 (14.9)	63.9 (12.24)
Donor	P = 0.385	P = 0.682	P = 0.119	P = 0.187	P = 0.109	P = 0.067	P = 0.070	P = 0.083
Matched sibling	25.8 (3.5)	19.6 (6.8)	21.3 (3.3)	22.9 (4.3)	89.6 (12.5)	32.1 (5.2)	121.7 (16.4)	80.8 (11.5)
Unrelated	24.8 (3.9)	18.0 (5.4)	19.1 (3.6)	20.1 (2.8)	82.2 (14.0)	28.8 (5.9)	110.9 (18.8)	73.8 (13.8)
Haploidentical family	23.6 (3.4)	17.9 (4.7)	18.6 (3.8)	17.7 (6.8)	77.7 (10.3)	26.0 (8.2)	103.7 (17.6)	67.3 (17.3)
Conditioning intensity	P = 0.356	P = 0.471	P = 0.908	P = 0.766	P = 0.553	P = 0.077	P = 0.317	P = 0.243
MAC	24.0 (4.1)	19.0 (3.1)	18.2 (5.1)	20.1 (6.0)	81.3 (14.7)	26.4 (6.5)	107.8 (20.6)	70.6 (14.8)
RIST	25.1 (3.6)	19.7 (3.8)	18.4 (5.8)	20.7 (6.6)	84.0 (13.3)	30.1 (5.9)	114.1 (18.0)	76.0 (13.8)
Conditioning regimen	P = 0.648	P = 0.773	P = 0.914	P = 0.896	P = 0.876	P = 0.311	P = 0.709	P = 0.725
BuCy	24.0 (4.1)	18.5 (5.9)	19.2 (3.4)	21.5 (5.0)	83.2 (15.6)	27.6 (6.2)	110.8 (21.5)	73.1 (13.7)
BuFlu	25.2 (3.8)	18.0 (6.0)	19.7 (3.8)	20.7 (6.0)	83.6 (13.4)	29.5 (6.0)	113.1 (18.1)	75.4 (13.8)
Others[a]	25.4 (3.5)	19.2 (4.9)	19.9 (3.7)	20.9 (7.9)	85.2 (12.7)	31.3 (5.2)	116.5 (16.8)	77.5 (13.5)
ATG	P = 0.977	P = 0.986	P = 0.471	P = 0.385	P = 0.499	P = 0.952	P = 0.653	P = 0.763
Yes	24.9 (3.7)	19.6 (3.7)	18.0 (5.6)	20.2 (6.6)	85.6 (13.7)	29.2 (6.0)	111.9 (18.5)	74.3 (13.7)
No	24.8 (4.1)	19.5 (3.5)	19.4 (5.8)	21.8 (5.7)	85.6 (13.4)	29.1 (7.1)	114.7 (19.7)	75.8 (15.8)
Acute GVHD, grade 2–4	P = 0.808	P = 0.895	P = 0.901	P = 0.469	P = 0.717	P = 0.979	P = 0.793	P = 0.696
Yes	24.8 (3.5)	20.1 (3.2)	18.4 (6.0)	19.9 (6.6)	83.2 (14.2)	29.8 (5.4)	113.0 (19.1)	74.5 (13.6)
No	25.1 (3.9)	20.2 (3.6)	18.1 (6.3)	21.5 (5.2)	85.0 (13.8)	29.7 (5.8)	114.7 (18.5)	76.3 (13.2)
Chronic GVHD	*P = 0.001**	P = 0.279	P = 0.842	P = 0.216	P = 0.060	P = 0.074	*P = 0.048**	*P = 0.024**
Yes	23.3 (4.20)	19.1 (3.96)	18.2 (5.80)	19.6 (5.73)	80.2 (14.20)	27.8 (6.12)	108.0 (19.51)	70.7 (14.3)
No	26.6 (2.17)	20.1 (3.20)	18.5 (5.44)	21.7 (6.99)	87.0 (12.13)	30.8 (6.04)	117.7 (16.52)	79.1 (12.8)
IST continuation	*P = 0.007**	P = 0.430	P = 0.415	P = 0.317	P = 0.072	*P = 0.023**	*P = 0.043**	*P = 0.033**
Yes	22.6 (3.8)	18.9 (3.6)	17.4 (4.7)	19.3 (6.1)	78.1 (12.7)	26.1 (6.0)	104.1 (17.9)	67.9 (14.2)
No	25.7 (3.4)	19.4 (3.7)	18.7 (6.0)	21.1 (6.6)	85.3 (13.7)	30.3 (6.0)	115.6 (18.3)	77.3 (13.5)

FACT-BMT, Functional Assessment of Cancer Therapy-Bone Marrow Transplantation; *PWB*, physical well-being; *SWB*, social/family well-being; *EWB*, emotional well-being; *FWB*, functional well-being; *FACT-G*, Functional Assessment of Cancer Therapy-General; *BMTS*, Bone Marrow Transplantation Subscale; *TOI*, Trial Outcome Index; *AML*, acute myeloid leukemia; *MDS*, myelodysplastic syndrome; *CML*, chronic myeloid leukemia; *AA*, aplastic anemia; *ALL*, acute lymphoblastic leukemia; *MAC*, myeloablative conditioning; *RIC*, reduced intensity conditioning; *BuCy*, busulfan plus cyclophosphamide; *BuFlu*, busulfan plus fludarabine; *ATG*, anti-thymocyte globulin; *GVHD*, graft-versus-host disease; *IST*, immunosuppressive therapy

*Means clinically significant ($P < 0.05$)

[a] Other regimens include fludarabine plus melphalan, cyclophosphamide plus melphalan, cyclophosphamide plus fludarabine, or cyclophosphamide or fludarabine

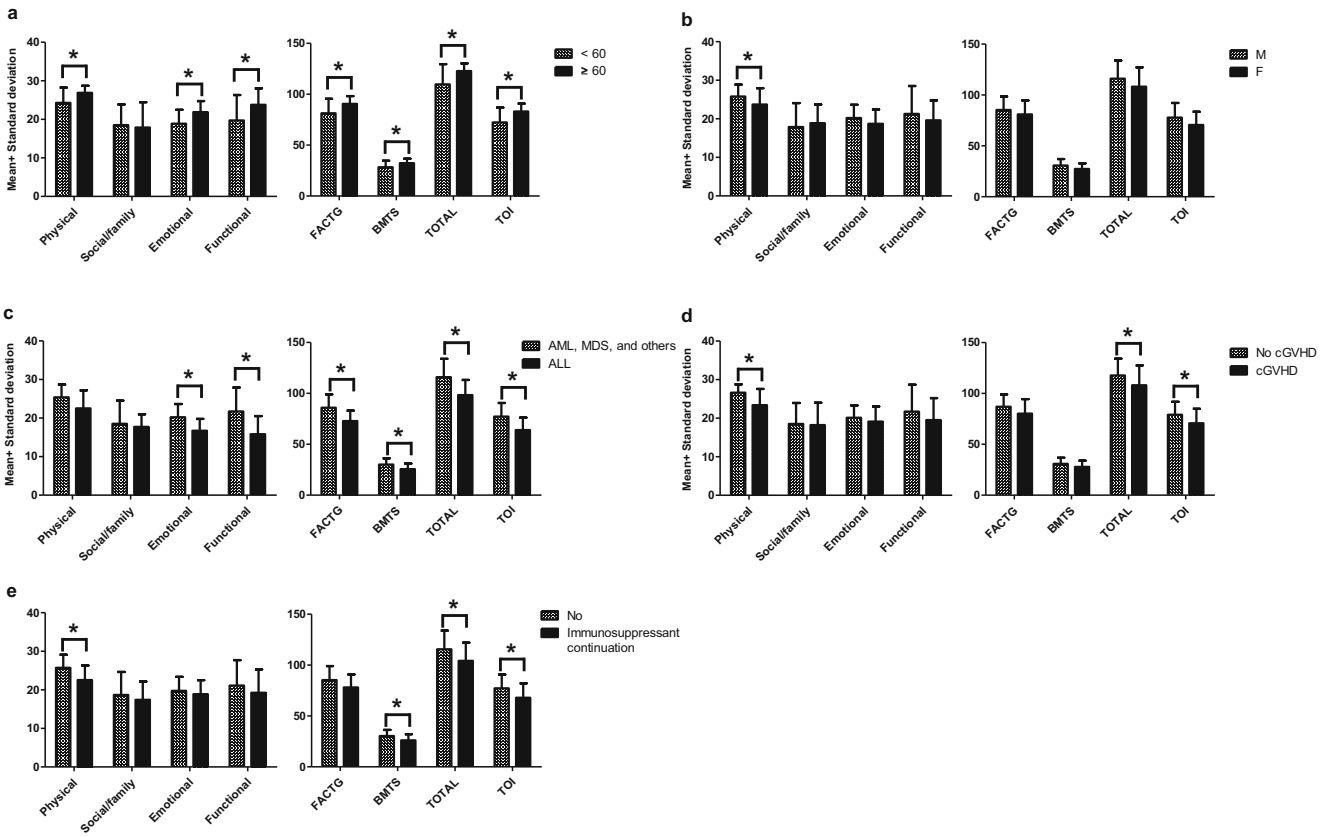

Fig. 1 Quality of life assessment using the Functional Assessment of Cancer Therapy-Bone Marrow Transplantation scale according to **a** age, **b** sex, **c** disease, **d** chronic GVHD, and **e** continuous immunosuppressant use. FACT-G, Functional Assessment of Cancer Therapy-General; BMTS, Bone Marrow Transplantation Subscale; TOI, Trial Outcome Index

noted in 42%, 22.5%, 18%, and 10.4% patients, respectively. Among included patients, 24% received HSCT from human leukocyte antigen (HLA)–matched sibling donors, 61% from unrelated donors, and 15% from haploidentical family donors. Reduced intensity conditioning (RIC) and myeloablative conditioning (MAC) regimens were administered in 75% and 25% patients, respectively. Anti-thymocyte globulin (ATG) was used in 76% of patients. After HSCT, all grades and grades 2–4 of acute GVHD were observed in 32.8% and 22.4% of patients, respectively. Chronic GVHD was observed in 54% of survivors. Immunosuppressive agents have been continuously administered to 28% HSCT survivors.

Patient-reported outcomes: symptoms and quality of life assessment

Table 2 represents symptom presentation categorized into organ systems among the included HSCT survivors. The most frequent symptom was fatigue (80.6% of patients). The mean brief fatigue inventory score was 3.2 (range, 0–10). The pain was observed in 23.9% of survivors. Headache, chest pain, dry eye, and conjunctival injection were observed in 13.4%, 14.9%, 37%, and 32.8% survivors, respectively. Oral mucosal problems such as dry mouth, gingivitis, and oral pain were noted in 22.4%, 23.9%, and 34.3% survivors, respectively. Additionally, insomnia, memory disturbance, and joint stiffness or pain were observed in 34.3%, 29.9%, and 20.9% survivors, respectively. HADS, NCCN DT, and QOL (FACT-BMT) data of all survivors are summarized in Table 2. Regarding the psychological aspect, anxiety (HADS-A score ≥ 8) and depression (HADS-D score ≥ 8) were detected in 14.9% and 13.6% survivors, respectively. Moreover, clinically significant distress (NCCN DT score ≥ 4) was observed in 10.4% of survivors.

Differences in quality of life (FACT-BMT) according to clinical factors

The QOL measurement by FACT-BMT was analyzed in subgroups for clinical factors (Table 3). Younger survivors (< 60 years) showed significantly worse QOL for physical ($P = 0.002$), emotional ($P = 0.006$), and functional well-being ($P = 0.014$), and Bone Marrow Transplantation Subscale (BMTS) ($P = 0.021$) and Total Outcome Index (TOI) ($P = 0.002$) except SFWB than elderly survivors (≥ 60 years). The differences in FACT-BMT by age groups are shown in Fig. 1. Female sex was significantly associated with lower PWB (mean, 23.7 vs. 25.8, respectively, $P = 0.046$) and BMTS

Table 4 Differences in fatigue, anxiety, depression, and distress according to criteria groups

	Fatigue		Anxiety (HADS-A)		Depression (HADS-D)		Distress (NCCN-DT)	
	Mean (SD)	*P* value	Mean (SD)	*P* value	Mean (SD)	*P* value	Mean (SD)	*P* value
Age, years		*P = 0.008**		*P = 0.001**		*P = 0.025**		P = 0.409
< 60	3.6 (2.45)		4.4 (3.32)		4.9 (3.30)		1.7 (1.75)	
≥ 60	1.7 (1.97)		1.7 (1.93)		2.9 (2.47)		1.2 (1.74)	
Sex		P = 0.197		P = 0.185		P = 0.252		P = 0.058
M	2.8 (2.2)		3.4 (3.2)		4.9 (3.6)		1.2 (1.6)	
F	3.7 (2.7)		4.5 (3.3)		4.0 (2.7)		2.1 (1.9)	
Diagnosis		P = 0.792		P = 0.057		*P = 0.028**		P = 0.167
AML, MDS, CML, AA, lymphoma	3.2 (2.6)		3.3 (2.8)		4.0 (2.91)		1.4 (1.7)	
ALL	3.3 (2.2)		5.6 (4.1)		6.5 (3.67)		2.2 (1.9)	
Donor type		P = 0.597		P = 0.637		P = 0.092		P = 0.659
Matched sibling	2.9 (2.7)		3.6 (2.8)		3.3 (3.0)		1.3 (1.3)	
Unrelated	3.4 (2.5)		4.1 (3.5)		4.6 (3.8)		1.7 (1.9)	
Haploidentical family	2.7 (2.1)		3.0 (2.6)		6.2 (4.6)		1.8 (1.5)	
Conditioning intensity		P = 0.482		P = 0.485		P = 0.861		P = 0.890
MAC	3.6 (2.7)		4.3 (3.0)		4.4 (4.3)		1.7 (1.7)	
RIC	3.1 (3.4)		3.7 (3.4)		4.6 (2.8)		1.6 (1.8)	
Conditioning regimen		*P = 0.008*		P = 0.747		P = 0.747		P = 0.379
BuCy	4.4 (3.0)		4.5 (2.6)		3.3 (2.0)		1.8 (1.9)	
BuFlu	2.3 (1.9)		3.1 (3.3)		4.7 (3.1)		1.2 (1.3)	
FluMel or CyFlu or Cy or Flu	4.4 (2.8)		3.4 (2.6)		4.0 (2.1)		1.6 (2.3)	
ATG		P = 0.693		P = 0.670		P = 0.834		P = 0.571
Yes	3.1 (2.3)		3.8 (3.4)		5.6 (2.8)		1.7 (1.7)	
No	3.4 (2.9)		4.1 (3.0)		4.3 (4.4)		1.4 (1.8)	
Acute GVHD (grades 2–4)		P = 0.353		P = 0.267		P = 0.215		P = 0.328
Yes	3.8 (3.1)		4.7 (3.3)		5.2 (3.3)		2.1 (2.1)	
No	3.0 (2.2)		3.5 (3.5)		4.0 (2.6)		1.5 (1.6)	
Chronic GVHD		P = 0.212		P = 0.556		*P = 0.015**		P = 0.719
Yes	3.6 (2.62)		4.1 (3.29)		5.4 (3.61)		1.7 (1.49)	
No	2.8 (2.21)		3.6 (3.31)		3.6 (2.29)		1.5 (2.03)	
Continuous immunosuppressant use		P = 0.787		P = 0.407		*P = 0.019**		P = 0.755
Yes	3.4 (2.5)		4.4 (2.9)		6.3 (3.8)		1.7 (1.3)	
No	3.2 (2.5)		3.7 (3.4)		3.9 (2.6)		1.6 (1.9)	

SD, standard deviation; *AML*, acute myeloid leukemia; *MDS*, myelodysplastic syndrome; *CML*, chronic myeloid leukemia; *AA*, aplastic anemia; *ALL*, acute lymphoblastic leukemia; *MAC*, myeloablative conditioning; *RIC*, reduced intensity conditioning; *BuCy*, busulfan plus cyclophosphamide; *BuFlu*, busulfan plus fludarabine; *FluMel*, fludarabine plus melphalan; *CyFlu*, cyclophosphamide plus fludarabine; *Cy*, cyclophosphamide; *Flu*, fludarabine; *ATG*, anti-thymocyte globulin; *GVHD*, graft-versus-host disease

*Means clinically significant ($P < 0.05$)

(mean, 27.3 vs. 30.7, respectively, $P = 0.036$) than male sex. Regarding disease types, ALL was associated with worse QOL than other diseases such as AML, MDS, CML, AA, and lymphoma. ALL survivors had significantly lower scores in emotional (mean, 16.7 vs. 20.2, respectively, $P = 0.004$) and functional well-being (mean, 15.8 vs. 21.8, respectively, $P = 0.002$) and general functional assessment of cancer therapy (mean, 72.8 vs. 85.9, respectively, $P = 0.002$), BMTS (mean, 25.5 vs. 30.1, respectively, $P = 0.029$), and TOI (mean, 63.9 vs. 77.2, respectively, $P = 0.006$) than those with other diseases.

On the contrary, no significant difference in QOL was noted by donor types such as matched sibling, unrelated, and haploidentical family donors. Moreover, conditioning intensity, types of conditioning regimens, and the use of ATG did not significantly affect QOL after HSCT. The history of acute

Table 5 Lifestyle and health screening status of hematopoietic stem cell transplantation survivors

	No. (%)
Body weight	
Gain/loss	27 (40.3)/6 (9.0)
Weight change	
1–2 kg	10 (14.9)
3–4 kg	18 (26.9)
≥ 5 kg	5 (7.5)
Exercise	
No	14 (20.9)
1–2/week	21 (31.3)
3–4/week	21 (31.3)
≥ 5/week	11 (16.4)
Job	35 (52.2)
Alcohol	
Current	12 (17.9)
Smoking	
Current	5 (7.5)
Past	32 (47.8)
Herbal medication or health supplement	19 (28.4)
Regular health screening	40 (59.7)

GVHD (grades 2–4) was not significantly associated with QOL. However, chronic GVHD had a significant adverse impact on QOL, specifically in PWB (23.3 vs. 26.6, respectively, $P = 0.001$) and TOI (70.7 vs. 79.1, respectively, $P = 0.024$). Similarly, continuous immunosuppressant use significantly adversely affected QOL including PWB ($P = 0.007$), BMTS ($P = 0.023$), and TOI ($P = 0.033$) (Fig. 1).

Risks of fatigue, anxiety, and depression according to clinical factors

Table 4 represents fatigue, anxiety (HADS-A), and depression (HADS-D) of HSCT survivors according to clinical factors. Younger survivors (< 60 years) showed a significantly higher tendency toward fatigue ($P = 0.008$), anxiety ($P = 0.001$), and depression ($P = 0.025$) than elderly survivors (≥ 60 years). ALL was significantly associated with higher depression scores than other diseases (AML, MDS, CML, AA, and lymphoma) (mean, 6.5 vs. 4.0, $P = 0.028$, respectively). Busulfan plus fludarabine regimen was significantly associated with lower fatigue scores than busulfan plus cyclophosphamide or other regimens (mean, 2.3 vs. 4.4, respectively, $P = 0.008$). Conditioning intensity, use of ATG, and donor types such as matched sibling, unrelated, and haploidentical family donors were not associated with fatigue, anxiety, depression, and distress. Depression risk was significantly associated with chronic GVHD (mean, 3.6 vs. 5.4, respectively, $P = 0.015$) and continuous immunosuppressant use (mean, 3.9 vs. 6.3, respectively, $P = 0.019$). However, the history of grades 2–4 of acute GVHD had no significant association with fatigue ($P = 0.353$), anxiety ($P = 0.267$), depression ($P = 0.215$), and distress ($P = 0.328$).

Lifestyle and health screening status

Table 5 represents the lifestyle and health screening status of survivors. Body weight gain and loss were observed in 40% and 9.0% of survivors, respectively. Regular exercise more than 3 times a week was performed in 47.7% of survivors, whereas 21% of survivors did not exercise at all. Moreover, 52.2% of survivors returned to their work, 17.9% of HSCT survivors were alcohol consumers, and 7.5% of survivors were current smokers even after HSCT. Furthermore, 28.4% of survivors have taken herbal medications or health supplements. A regular health screening test has been conducted only in 59.7% of survivors.

Discussion

We found the unmet needs of 67 survivors undergoing HSCT over 2 years in terms of physical and psychological problems, QOL, lifestyle, and healthcare. Fatigue was the most common symptom (80.6% of survivors). The etiology may be multifactorial, including reduced physical activity and adverse side effects of taking medications after HSCT [22]. Additionally, late effects such as pain and discomfort after HSCT were manifested in most body organs (Table 2). Clinically meaningful distress was observed in 10.4% of survivors. According to HADS scores ≥ 8, anxiety and depression were observed in 14.9% and 13.6% survivors, respectively. Besides, we found that insomnia and memory disturbance was significant in more than one-third of survivors.

Previous studies regarding late complications and QOL in long-term survivors have been mostly conducted in children or young adult patients who underwent HSCT with MAC [11, 23]. However, in our data, the median age of survivors was 45 years. Moreover, the majority of patients (74.7%) were treated with RIC. Regarding conditioning intensity, long-term QOL after HSCT was comparable between the MAC and RIC groups. Clavert et al. reported similar results in a study of 100 adult patients who underwent RIC HSCT [24]. Moreover, no significant differences between the MAC and RIC groups were noted [13, 14, 25]. RIC patients are expected to experience good QOL in the early post-transplantation period because of lower regimen-related toxicities, and an impaired QOL might be observed in the later post-transplantation period because of high rates of chronic GVHD [24]. However, patients treated with MAC experienced more fatigue than those with RIC.

In a study of 155 patients with AML or ALL undergoing HSCT at CR status, Bonifazi et al. reported that the ATG group had better survival rates without relapse than the no-ATG group [26]. However, we showed that ATG use was not associated with long-term QOL, fatigue, anxiety, depression, and distress after HSCT. In recent years, HSCT with unrelated or haploidentical donors as well as HLA-matched sibling donors have significantly increased [27]. No significant differences in QOL among donor types such as matched sibling, unrelated, or haploidentical familial donors were noted.

Interestingly, younger age (< 60 years) was more significantly associated with poor QOL (FACT-BMT score) and a higher risk of fatigue than older age (≥ 60 years). Generally, elderly patients are considered to have more comorbidity than younger patients, but QOL and fatigue were not associated with comorbidity in our data. Younger survivors (< 60 years) showed more anxiety and depression than elderly survivors, and this might influence their QOL and fatigue negatively. Associations between anxiety or depression and QOL were demonstrated in several previous studies [28, 29].

ALL survivors showed significantly higher depression score (HADS-D) and worse QOL score (FACT-BMT) than those with other diseases. It might be because patients with ALL could usually be treated with more intensive chemotherapies than other diseases including AML, MDS, and AA. In a recent study, Haykawa et al. showed that glucocorticoid therapy was a risk factor for decreased body mass index, delayed recovery of muscle strength, and avascular necrosis [10, 30]. More use of glucocorticoid usually combined with chemotherapy regimens for ALL might adversely affect QOL, although we could not analyze glucocorticoid use among the survivors. Major depression is a possible risk factor for survival after HSCT [31]. Psychological problems such as anxiety and depression are easily underestimated during the HSCT treatment period. Therefore, regular screening and management for psychological problems including anxiety, depression, insomnia, and memory disturbance are important to improve QOL for survivors post-HSCT.

Moreover, the significant adverse factors affecting QOL and depression after HSCT were chronic GVHD and continuous immunosuppressant use, whereas severe acute GVHD was not associated with long-term QOL after HSCT. The negative impact of chronic GVHD on QOL has been reported [9, 10, 24]. However, patients with resolved chronic GVHD had comparable QOL with survivors who had never been diagnosed with chronic GVHD [9]. Therefore, chronic GVHD management is important to improve QOL for HSCT survivors. In chronic GVHD, the eye and mouth are the most commonly involved sites, and more than one-third of survivors showed eye and oral problems including dryness or pain, consistent with a recent review article [8]. Therefore, regular consultation with ophthalmologists and dentists is recommended for HSCT survivors. Chronic GVHD can result in joint destruction and associated pain and loss of range of motion [30]. Joint stiffness or pain caused by chronic GVHD needs regular examination by physicians. Moreover, active physical therapy after HSCT can be beneficial for muscle relaxation and strength [30].

Additionally, compared with male, female survivors showed significantly worse PWB and higher distress ($P = 0.046$ and $P = 0.05$, respectively). Impairment of PWB on QOL questionnaires was associated with the most altered exercise capacity and the degree of physical health impairment [32, 33]. In previous studies on exercise programs after HSCT, fatigue, aerobic capacity, muscle strength, and QOL were improved [34]. Therefore, controlling physical symptoms and creating programs to improve exercise capacity might be important to improve QOL, specifically for female survivors.

Reduced exercise capacity has been associated with fatigue, disability, and poor QOL [17, 35]. Dirou et al. reported that a high proportion (75.4%) of HSCT survivors had mild to severe exercise capacity impairment at 1-year post-HSCT. Significant improvements in QOL and potential physiological and psychosocial benefits have been reported after HSCT in the previous exercise intervention studies by Juan et al. [36] and Bogg et al. [37]. Therefore, exercise or physical therapy is routinely recommended before, during, and after HSCT aimed at improving QOL, reducing disease burden, improving physical function, assisting reintegration to social activities, and returning to work and normal activities of daily life [30]. In this study, 52.2% of survivors did not exercise sufficiently (no exercise or 1–2 times a week) after HSCT; regular exercise (3–5 times a week) should be advised for HSCT survivors to reduce fatigue and improve QOL.

Gastrointestinal side effects including GI GVHD can be observed during HSCT, and malnutrition and weight loss after HSCT may occur; thus, adequate nutritional support is emphasized to the survivors [38]. However, it should be also educated that the beneficial effects of most herbal medications or health supplements were not demonstrated, because 28.4% of survivors administered herbal medication or health supplements as shown in our data.

Among survivors, 7.5% and 17.9% were current smokers and alcohol consumers survivors, respectively. To prevent late comorbidity and secondary malignancies, survivors need to be continuously educated to stop smoking and drinking alcohol. Low QOL and depression are associated with a higher risk of smoking and higher difficulties of smoking cessation [39]. Therefore, the

screening and management of depression would be helpful for HSCT survivors to quit smoking. Moreover, regular health screening tests for late complications and secondary malignancies had not been conducted in 40% of HSCT survivors. Therefore, education for lifestyle modification such as regular exercise, diet, and smoking and alcohol cessation, and regular health screening should be incorporated when creating a survivorship care plan for HSCT survivors. In this study, employment after HSCT was maintained in 52.2% of survivors. High unemployment might affect healthcare status and compliance for monitoring secondary malignancies and relapse and might result in socioeconomic problems and distress. Hence, consultations with the social welfare team are essential when creating a survivorship care plan.

To our knowledge, this is the first study of PRO using a tablet PC during routine survivorship care for HSCT survivors. There are some limitations that this is not a prospective study. Nevertheless, we have routinely conducted a general assessment regarding the physical, psychological, and socioeconomic aspects, QOL, and lifestyle for over 2 years in non-relapse HSCT patients. Hundreds of questionnaires assessing whole organ problems, depression, anxiety, QOL, and lifestyle can be easily screened and assessed using a tablet PC approximately 30 min before meeting a physician in real practice. The survey of PRO using a tablet PC for HSCT survivors is considered an easy and fast method, although it is sometimes not applicable for elderly patients who have a visual impairment or not used to dealing with a tablet PC.

In conclusion, younger age (< 60 years), female, ALL, chronic GVHD, and continuous immunosuppressant use are high risk factors for poor QOL and depression. Considering our understanding regarding the risk factors of late effects and unmet needs for HSCT survivors, we have to build a more active patient-directed survivorship care plan after HSCT.

Author Contribution Yunsuk Choi, Jaekyoung Cheon, Jae-Cheol Jo, SuJin Koh, and Young Ju Min contributed to the study conception and design. Patient management and data collection were performed by Jaekyoung Cheon, Yoo Jin Lee, Jae-Cheol Jo, Kukju Kweon, Sang-Hyuk Park, Sin-hye Lee, and Hyo-jin Kim. Data analysis was performed by Yunsuk Choi and Jaekyoung Cheon. The first draft of the manuscript was written by Yunsuk Choi and Jaekyoung Cheon. All authors reviewed the manuscript and contributed to the editing of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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