DOCTORAL THESIS

Clinical impact of cigarette smoking on the outcomes of allogeneic hematopoietic stem cell transplantation: A multicenter retrospective study

（喫煙が同種造血幹細胞移植に与える影響
:多施設共同後方視的研究）

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ARTICLE

Clinical impact of cigarette smoking on the outcomes of allogeneic hematopoietic stem cell transplantation: a multicenter retrospective study

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Smoking is associated with a high risk for different diseases including respiratory tract infections in immunocompetent patients. However, data about the effects of cigarette smoking on the outcomes of allogeneic hematopoietic stem cell transplantation (allo-HSCT) are limited. Therefore, we retrospectively investigated 608 patients aged ≥20 years with hematological disorders who received their first allo-HSCT at our group of hospitals between 2000 and 2015, and evaluated the impact of cigarette smoking before allo-HSCT on clinical outcomes by dividing patients into two groups according to the Brinkman index (BI) (nonsmokers or light smokers [BI: 0–500] and heavy smokers [BI: ≥ 500]). Multivariate analyses showed that heavy smoking was associated with a high 5-year cumulative incidence of chronic graft-versus-host disease (cGVHD) (hazard ratio [HR]: 1.73, 95% confidence interval [CI]: 1.15–2.61, $p < 0.01$). The 5-year overall survival (HR: 1.16, 95% CI: 0.86–1.58, $p = 0.33$) and disease-free survival (HR: 1.12, 95% CI: 0.83–1.52, $p = 0.45$) were similar between the two groups. Hence, cigarette smoking is correlated with cGVHD, although prospective studies must be conducted to further verify this result.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is widely used to treat patients with hematological disorders. Although it is commonly used, transplantation-related mortality and morbidity rates remain high. Pulmonary complications can occur after transplantation and can be fatal [1, 2]. However, data about the effects of cigarette smoking on transplantation outcomes are limited. Previous studies have reported that smoking is correlated with posttransplant pulmonary complications. However, they are limited to a subset of cases, and the clinical effects of smoking on pulmonary and other posttransplant complications have not been fully explored [3–6]. Increasing number of studies have shown that smoking impairs immune function, exacerbates chemotherapy-related toxicity, and increases the risk of recurrence and secondary malignancies. However, information about the effects of smoking history on transplantation-related complications is limited [7–12]. Therefore, we conducted a multicenter retrospective study to evaluate the correlation between smoking history, respiratory function and posttransplant outcomes.

METHODS

Study design

This multicenter, investigational study used the clinical research data of the Yokohama Cooperative Study Group for Hematology (YACHT). It included patients aged ≥20 years who initially received allo-HSCT at Yokohama City University Medical Center, Kanagawa Cancer Center, and Yokohama City University Hospital between 2000 and 2015. Data about the demographic characteristics of patients, such as smoking history, results of pulmonary function test (PFT), and pulmonary complications, were collected. Information regarding smoking was obtained from the medical history record. Low-risk disease was defined as acute myeloid leukemia (first/second remission), acute lymphoblastic leukemia (first remission), chronic myeloid leukemia (first chronic phase), lymphoma (remission), refractory and aplastic anemia, and myelodysplastic syndrome (refractory anemia/refractory anemia with ringed sideroblasts). High-risk disease was defined as the other conditions that are not included in low-risk disease.

The stem cell sources were classified as follows: related bone marrow, unrelated bone marrow, related peripheral blood stem cells, and cord blood. The donor match status was determined according to donor–recipient human leukocyte antigen (HLA) compatibility. The conditioning regimens were categorized as myeloablative and reduced intensity [13]. Acute graft-versus-host disease (GVHD) was defined according to the consensus criteria [14]. Meanwhile, chronic GVHD (cGVHD) was classified according to the standard criteria [15]. Previous studies have shown that a Brinkman index (BI; average daily smoking volume [number of cigarettes] × years of smoking) of >400 indicates a high risk of developing lung cancer, and a BI of >600 suggests chronic obstructive pulmonary disease and respiratory disease. Therefore, we divided patients into two groups according to BI: nonsmokers or light smokers (BI: 0–500, $n = 520$; defined as low BI) and heavy smokers (BI: ≥ 500, $n = 88$; defined as high BI). The transplantation outcomes of the two groups including PFT results were compared. All pulmonary function values, except the forced expiratory volume in 1 s (FEV_1)-to-forced vital

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Table 1. Patient characteristics.

	0 ≦ BI < 500 *N* (%)	BI ≧ 500 *N* (%)	*p* value
Age, mean (range)	44.6 y (20–68)	53.9 y (37–67)	<0.01
Sex			<0.01
M	267 (51)	80 (91)	
F	253 (49)	8 (9)	
PS			0.63
0	490 (94)	82 (93)	
1	30 (6)	6 (7)	
HCT-CI			0.43
0–3	469 (90)	77 (88)	
4–5	34 (7)	9 (10)	
6-	17 (3)	2 (2)	
Diagnosis			
AML	289 (56)	60 (68)	
ALL	120 (23)	7 (8)	
MDS	44 (9)	11 (12)	
ML	26 (5)	7 (8)	
MPN	9 (2)	2 (2)	
CML	28 (5)	2 (2)	
Other	3 (<1)	0 (0)	
Disease risk			<0.01
Standard risk	371(71)	61 (69)	
High risk	149(29)	27 (31)	
Donor source			0.51
RBM	112 (22)	16 (18)	
RPB	75 (14)	11 (12)	
UBM	220 (42)	41 (48)	
UCB	113 (22)	20 (22)	
Conditioning therapy		0.02	
MAC	352 (68)	47(53)	
RIC	168 (32)	41(47)	
HLA (except CBT)		0.95	
Matched	251 (48)	40 (45)	
Mismatched	156 (30)	28 (32)	
GVHD prophylaxis		0.88	
CyA±MTX	174 (33)	29 (34)	
TAC ± MTX	346 (67)	59 (66)	
ABO disparity			0.78
Major mismatch	141 (27)	24 (27)	
Minor mismatch	149 (29)	21 (24)	
Both	40 (8)	6 (6)	
TBI ≧2 Gy			0.76
Yes	429 (83)	72 (82)	
No	91 (17)	16 (18)	

BI Brinkman index, *M* male, *F* female, *PS* performance status, *HCT-CI* hematopoietic cell transplant-comorbidity index, *AML* acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *MDS* myelodysplastic syndrome, *ML* malignant lymphoma, *MPN* myeloproliferative neoplasms, *CML* chronic myeloid leukemia, *RBM* related bone marrow, *RPB* related peripheral blood, *UBM* unrelated bone marrow, *UCB* umbilical cord blood, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *HLA* human leukocyte antigen, *TBI* total body irradiation.

Table 2. Characteristics of smoking.

	0 ≦ BI < 500 *N* (%)	BI ≧ 500 *N* (%)	*p* value
Cigarettes smoked per day			
0	342 (66)	0	
1–9	22 (4)	0	
10–19	73 (14)	5 (6)	
20–39	80 (15)	65 (74)	
≧40	3 (1)	18 (20)	
Brinkman Index			
0	342 (66)		
1–299	132 (25)		
300–499	46 (9)		
500–799		54 (61)	
800–999		16 (19)	
≧1000		18 (20)	
Time since quitting smoking			
<1 yr (Current smoker)	63 (12)	31 (35)	<0.01
1–10 yr	59 (11)	36 (41)	<0.01
10–19 yr	18 (3)	9 (10)	<0.01
≧20 yr	22 (4)	2 (2)	0.42
Unknown	16 (3)	10 (11)	

Brinkman Index: average daily smoking volume [number of cigarettes] × years of smoking.
Current smoker: patients who smoked until the year of transplantation.

capacity ratio, were expressed as percentage of the predicted values according to published equations, unless otherwise specified. The diffusing capacity for carbon monoxide (DLCO) measurements was corrected for hemoglobin levels obtained at the closest time to the assessment. PFT was routinely performed at pretransplantation and approximately 1-year post transplantation.

Statistical definitions and analytical methods

The baseline characteristics of patients and the incidence of GVHD were compared between the smoking groups using Fisher's exact test for categorical data and the Mann–Whitney *U* test for continuous variables. The Kaplan–Meier technique was used to analyze the probability of overall survival (OS) and disease-free survival (DFS). To compare OS and DFS, the log-rank test and Cox proportional hazard model were utilized for univariate and multivariate analyses, respectively. For the analyses of OS, death from any cause was considered an event, and the survivors were censored during the last follow-up. For the analyses of DFS, relapse or death was considered an event. The cumulative incidences of relapse, nonrelapse mortality (NRM), and GVHD were evaluated using the Fine–Gray model for univariate and multivariate analyses. In the NRM analysis, relapse was considered a competing risk. We applied the backward-stepwise selection algorithm and retained the statistically significant variables, in addition to those that were affected in the multivariate analysis in previous reports. A p value of <0.05 was considered statistically significant. In the secondary analyses, the Mann–Whitney *U* test was used to examine the association between smoking dose and pulmonary function after 1 year. This study was conducted after it was approved by the institutional review board of each institution. All statistical analyses were performed using EZR version 1.54, a graphical user interface for R version 3.5.2 [16].

RESULTS

Clinical characteristics of participants

In total, 608 patients were eligible for the study. Table 1 shows the characteristics of patients who were divided into the low- and

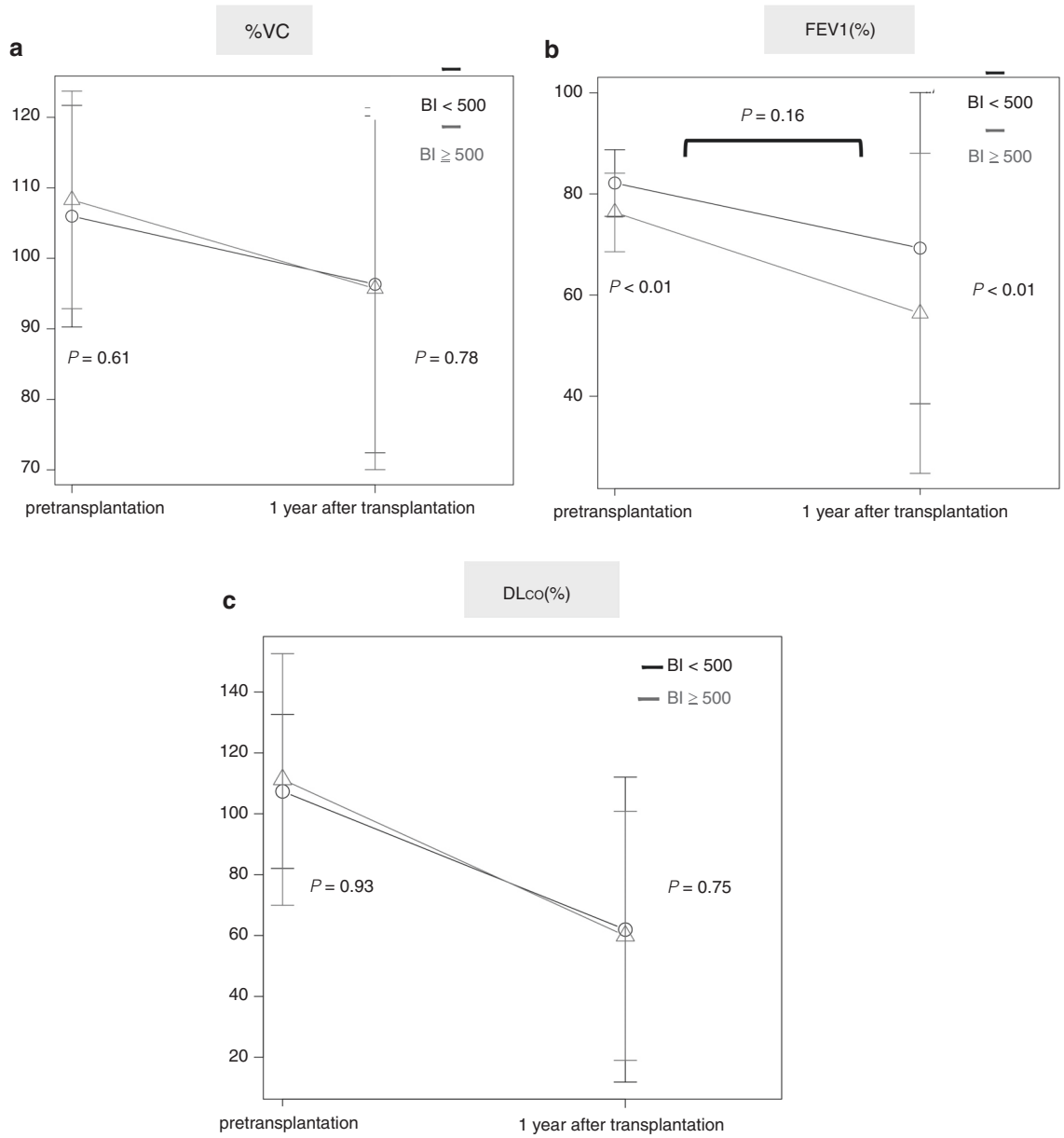

Fig. 1 PFT results at pretransplantation and 1 year post transplantation. Data were presented using orthodontic information (**a** %VC **b** FEV_1 **c** DLCO). The FEV_1, %VC, and DLCO were expressed as percentage of the predicted values. PFT pulmonary function test, FEV_1 forced expiratory volume in 1 s; %VC percentage of vital capacity, DLCO diffusing capacity for carbon monoxide.

high-BI groups. The mean ages of the high and low-BI groups were 54 and 45 years, respectively. Among 88 patients with high BI, 91 (%) patients were male, 31 (%) patients had high-risk disease, and 87 (%) patients used reduced-intensity conditioning (RIC) regimen. The two groups did not significantly differ in terms of donor HLA and ABO matching, performance status (PS), hematopoietic cell transplant-comorbidity index (HCT-CI), and stem cell source. Table 2 shows smoking status of the patients. Most patients in the High-BI group smoked more than 20 cigarettes a day, and a higher proportion smoked up to 1 year before transplantation. Figure 1 depicts the results of PFT at pretransplantation and 1 year post transplantation. The percentage of vital capacity (%VC) and DLCO (%) was not significantly different between the low- and high-BI groups either at pre- or posttransplantation (Fig. 1a, c). In contrast, the high-BI group had a lower FEV_1 (%) than the low-BI group both at pre- and posttransplantation ($p < 0.01$) (Fig. 1b). The time-dependent changes of %VC, DLCO (%), and FEV_1 (%) between pre- or posttransplantation did not significantly differ between the two groups. The median follow-up period after allo-HSCT was 1971 days.

OS, DFS, and NRM

The high-BI group had a lower 5-year OS (52% vs. 39%, $p = 0.01$, Fig. 2a) and 5-year DFS (47% vs. 37%, $p = 0.03$, Fig. 2b) than the low-BI group by univariate analysis. However, the 5-year NRM did not significantly differ between the low BI and the high BI groups (24% and 34%, respectively, $p = 0.11$) (Fig. 2c). Similarly, there was no significant difference in terms of the 5-year relapse rate between the low-BI and the high BI groups (35% and 40%, respectively, $p = 0.19$) (Fig. 2d).

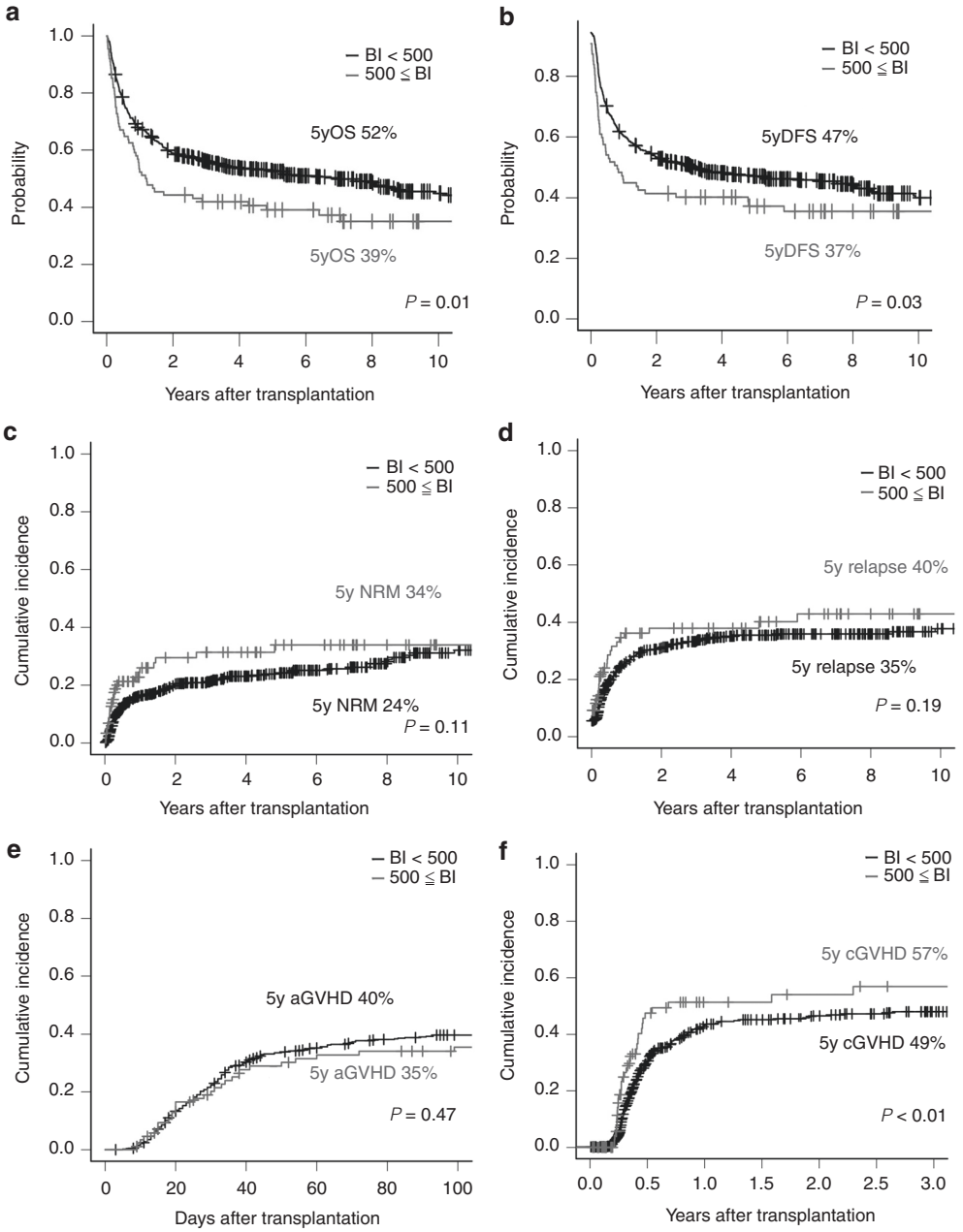

Fig. 2 Survival probability and cumulative incidence of relapse and GVHD. a Probability of OS. **b** Probability of DFS. **c** Cumulative incidence of NRM. **d** Cumulative incidence of relapse. **e** Cumulative incidence of acute GVHD. **f** Cumulative incidence of chronic GVHD. OS overall survival, DFS disease-free survival, NRM nonrelapse mortality, GVHD graft-versus-host disease.

Incidence of GVHD

The absolute 5-year incidence of acute GVHD (aGVHD) did not significantly differ between the low-BI and the high BI groups (40% and 35%, respectively, $p = 0.47$) (Fig. 2e). In contrast, the absolute 5-year incidence of cGVHD was significantly lower in the low-BI group than in the high BI group (49% and 57%, respectively, $p < 0.01$) (Fig. 2f). We initially speculated that smoking is associated with lung complications including cGVHD of the lungs. Interestingly, however, there was no significant association between smoking and the incidence of cGVHD in the lungs (21% and 24%, respectively, $p = 0.19$) (Supplementary Fig. 1a) and between smoking and the incidence of bronchopneumonia (15% and 23%, respectively, $p = 0.26$) (Supplementary Fig. 1b).

We went on to analyze the difference of cGVHD incidence in 'current smoker (patients who kept smoking until the year of transplantation) vs. non-current smoker' or 'smoker vs. never-smoker (BI = 0)' settings. Comparison of current vs. non-current smokers revealed no statistical difference in cGVHD both in low-BI and high-BI groups (Supplementary Fig. 2a–c). It should be noted, however, that the incidence of cGVHD tended to be higher in current smokers, although not statistically significant ($p = 0.13$), among high-BI group, suggesting that early cessation of smoking might be beneficial for patients with high-BI (Supplementary Fig. 2c). We have also compared the incidence of cGVHD by stratifying patients according to the time since smoking cessation (Supplementary Fig. 3a, b). Again, we observed a similar, statistically non-significant reduction of cGVHD incidence in non-current smokers with high BI, but not in those with low-BI. Comparison of smokers and never-smokers showed no difference in cGVHD incidence both in overall patients and low-BI group (Supplementary Fig. 4a, b).

Table 3. Causes of death after HSCT.

	0 ≦ BI < 500 *N* (%)	BI ≧ 500 *N* (%)	*p* value
Documented infection			
Fungal	4 (1)	1 (1)	0.87
Bacterial	26 (5)	10 (11)	0.09
Viral	4 (1)	1 (1)	0.87
GVHD			
Acute	13 (3)	3 (3)	0.88
Chronic	4 (1)	1 (1)	0.87
Interstitial pneumonia	25 (5)	3 (3)	0.31
Relapse	109 (21)	21 (24)	0.67
Secondary malignancy	5 (1)	1 (1)	0.97
Rejection/poor graft function	6 (1)	2 (2)	0.58
Multi-organ failure	16 (3)	4 (5)	0.74
VOD/SOS	12 (2)	2 (2)	0.76
bleeding	7 (1)	3 (3)	0.31
Other	12 (2)	1 (1)	

HSCT hematopoietic stem cell transplantation, *GVHD* graft-versus-host disease, *VOD* veno-occlusive disease, *SOS* sinusoidal obstruction syndrome.

Cause of death

Table 3 shows the direct causes of death after HSCT. In total, 298 patients ($n = 245$ in the low-BI group and $n = 53$ in the high-BI group) died, and relapse was the most common cause of death. The high BI group was more likely to have a higher incidence of fatal bacterial infections. However, there were no significant differences between the low-BI and the high-BI groups in terms of the incidence of fatal interstitial pneumonia or cGVHD.

Univariate and multivariate analysis

Table 4 depicts the results of the univariate analysis of OS, DFS, NRM, and incidence of acute or chronic GVHD. Age ≥50 years, low or high disease risk, donor source (RBM, RPB, UBM, or UCB), HCT-CI (low, intermediate, or high), history of lung infection before HSCT (yes or no), and BI were associated with OS and DFS. Furthermore, age > 50 years, low- or high-disease risk, donor source, and BI were correlated with the incidence of cGVHD.

Table 4 also shows the results of the multivariate analysis. In the analysis adjusted for age, disease risk, stem cell source, HCT-CI, and lung infections, high BI was not associated with a higher risk of OS (hazard ratio [HR]: 1.16, 95% confidence interval [CI]: 0.9–1.6, $p = 0.33$) or DFS (HR: 1.12, 95% CI: 0.8–1.5, $p = 0.45$). Similarly, in the analysis adjusted for age, HLA, stem cell source, HCT-CI, and lung infections, smoking dose was not associated with a higher risk of NRM (HR: 1.04, 95% CI: 0.6–1.9, $p = 0.9$). In the analysis adjusted for stem cell source and HLA, smoking dose was not correlated with a higher absolute 5-year incidence of acute GVHD (HR: 0.99, 95% CI: 0.6–1.5, $p = 0.95$). In contrast, in the analysis adjusted for age, disease risk, stem cell source, and HLA, the low-BI group had a significantly lower absolute 5-year incidence of cGVHD than the high BI group (HR: 1.73, 95% CI: 1.2–2.6, $p < 0.01$).

Characteristics of cGVHD

Table 5 shows the characteristics of cGVHD divided according to low and high BI. As described earlier, heavy smoking did not significantly increase the incidence of chronic lung GVHD ($p = 0.19$). Instead, the incidence of cGVHD in skin was significantly higher in high BI group, and cGVHD in mouth and gastrointestinal tract tended to be more frequent, although not statistically significant, in high BI group. The extent of cGVHD as well as the frequency of patients requiring various immunosuppressive therapies for cGVHD were not significantly different between the two groups.

DISCUSSION

Smoking has been reported to be associated with a high incidence of malignancies and cardiac and pulmonary diseases [17]. Some studies have shown that smokers are at high risk for treatment-related mortality and disease recurrence. Others have reported smoking leads to an increased risk for early pulmonary complications after transplantation. On the other hand, some studies did not show such an association [3, 18, 19]. In this study, we demonstrated that heavy smoking was associated with a high risk for cGVHD. Sub-group analysis showed that only a skin cGVHD significantly increased in patients with high BI. However, we noticed a slight, non-significant increase in cGVHD also in other organs such as mouth, gastrointestinal tract, and liver in high-BI group, and we speculate these small differences eventually led to an overall increase in 5-year incidence of cGVHD in high-BI patients. Of note, there was no difference in the severity and treatment of cGVHD between the low and high BI groups. It is also intriguing that heavy smoking did not affect the incidence of cGVHD in the lungs and pulmonary infections. This may suggest that chronic pulmonary inflammation induced by smoking does not serve as a major accelerator of cGVHD or infections in the lung.

Previous study has shown that smoking is correlated with a shorter survival after transplantation and a higher incidence of recurrence [3]. However, our study demonstrated that OS, DFS or relapse adjusted for age, disease risk, donor source, HCT-CI, and lung infection was similar between the high and low-BI groups. This could be attributed to the patient selection bias by which physicians did not allow patients with severe pulmonary dysfunction to undergo HSCT. This notion is, in fact, supported by the finding that posttransplant decline of %VC, FEV1% or DLco was not statistically different between patients with low-BI and high BI.

Previous study has shown the important role for B cells in the pathogenesis of chronic GVHD (cGVHD) and patients with cGVHD have elevated B-cell activating factor (BAFF) to B-cell ratios compared to patients without cGVHD [20]. On the other hand, human and mouse studies have shown that smoking increases BAFF levels not only in the lungs but also in other organs including the spleen [21, 22]. Taken together, we speculate that smoking activates B cells by increasing the level of BAFF, thereby increases the incidence of cGVHD. This notion may also explain the systemic effect of smoking on cGVHD, which increases the incidence of cGVHD in non-pulmonary site, such as skin. This hypothesis must be confirmed by future investigation.

cGVHD and pretransplantation pulmonary dysfunction are a risk factor for posttransplant respiratory failure [23]. Nonetheless, smoking itself has not been considered a risk for cGVHD. In this respect, the results from this study are remarkable, and therefore, we recommend that patients should quit smoking as soon as they decide to undergo transplantation. In addition, we should be cautious about cGVHD in patients with high BI after HSCT. According to a multivariate analysis showing a higher risk of mismatched donor and a lower risk of cord blood transplantation, if an HLA-identical sibling is not available, cord blood may be a favorable option to a mismatched family donor or an unrelated donor among patients with a high BI.

This study has some limitations. Considering its retrospective nature, some pulmonary complications might have been missed despite a detailed database and extensive chart review. For example, we could have picked up and analyzed only the first episode of multiple pulmonary events, and the incidence of late-onset pulmonary complications could have been underestimated. Further, we could not monitor the smoking status of patients after allo-HSCT,

Table 4. Univariate and Multivariable Analysis for Outcome.

Variables	Factors	OS[a]						
		Univariate analysis				Multivariable analysis		
		n	5yOS	95% CI	*P*	HR	95% CI	*P*
Age	<50	263	55.9%	0.50–0.61	<0.01	1		
	≧50	345	43.5%	0.33–0.45		1.34	1.05–1.71	0.05
Sex	M	347	49.8%	0.44–0.55	0.39			
	F	261	51.5%	0.45–0.57				
Disease risk	Low	432	62.3%	0.57–0.67	<0.01	1		
	High	176	32.2%	0.24–0.36		2.12	1.69–2.66	<0.01
Conditioning	MAC	399	51.0%	0.43–0.57	0.67			
	RIC	209	50.3%	0.45–0.55				
HLA	Match	270	53.6%	0.45–0.61	0.28			
	Mismatch	168	47.4%	0.41–0.53				
Donor	RBM	128	61.4%	0.52–0.69	0.01	1		
	RPB	86	47.7%	0.41–0.53		1.39	0.94–2.05	0.09
	UBM	261	46.4%	0.34–0.57		1.48	1.08–2.03	0.02
	UCB	133	46.6%	0.37–0.55		1.41	0.98–2.03	0.06
HCT-CI	0–3	548	52.9%	0.48–0.57	<0.01	1		
	4–5	43	31.7%	0.18–0.46		1.64	1.11–2.44	0.02
	6-	17	23.5%	0.07–0.45		1.62	0.92–2.85	0.09
Lung infection	Yes	52	20.2%	0.10-0.32	<0.01	2.48	1.78–3.45	<0.01
	No	556	53.1%	0.48–0.57		1		
BI	0 ≦ BI < 500	520	52.5%	0.48–0.57	0.01	1		
	BI ≧ 500	88	39.1%	0.29–0.49		1.16	086–1.58	0.33
Variables	**Factors**	**DFS[b]**						
		Univariate analysis				**Multivariable analysis**		
		n	**5yDFS**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age	<50	263	50.2%	0.44–0.55	<0.01	1		
	≧50	345	39.7%	0.33–0.45		1.3	1.03–1.64	0.03
Sex	M	347	45.6%	0.40–0.51	0.69			
	F	261	45.6%	0.39–0.51				
Disease risk	Low	432	54.9%	0.49–0.60	<0.01	1		
	High	176	30.5%	0.24–0.36		1.9	1.52–2.37	<0.01
Conditioning	MAC	399	46.0%	0.40–0.51	0.73			
	RIC	209	44.5%	0.37–0.51				
HLA	Match	270	43.4%	0.37–0.49	0.4			
	Mismatch	168	48.3%	0.41–0.55				
Donor	RBM	128	52.2%	0.43–0.60	0.14	1		
	RPB	86	44.7%	0.38–0.50		1.16	0.79–1.69	0.45
	UBM	261	38.9%	0.27–0.50		1.24	0.92–1.67	0.16
	UCB	133	42.6%	0.33-0.51		1.17	0.83–1.65	0.36
HCT-CI	0–3	548	46.7%	0.43–0.52	<0.01	1		
	4–5	43	28.6%	0.16–0.43		1.63	1.11–2.41	0.01
	6-	17	23.5%	0.07–0.45		1.44	0.82–2.54	0.2
Lung infection	Yes	52	14.3%	0.06–0.26	<0.01	2.32	1.67–3.22	<0.01
	No	556	48.6%	0.43–0.53		1		
BI	0 ≦ BI < 500	520	47.1%	0.43–0.51	0.03	1		
	BI ≧ 500	88	37.2%	0.27–0.47		1.12	0.83–1.52	0.45
Variables	**Factors**	**NRM[c]**						
		Univariate analysis				**Multivariable analysis**		
		n	**5yNRM**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age	<50	263	22.9%	0.18–0.28	<0.01	1		

Table 4. continued

Variables	Factors	OS[a]						
		Univariate analysis				Multivariable analysis		
		n	5yOS	95% CI	*P*	HR	95% CI	*P*
	≧50	345	30.2%	0.23–0.36		1.83	1.23–2.71	<0.01
HLA	Match	270	23.1%	0.18–0.28	0.02	1		
	Mismatch	168	29.1%	0.20–0.37		1.49	1.00–2.22	0.05
Donor	RBM	128	13.4%	0.07–0.20	<0.01	1		
	RPB	86	33.1%	0.20–0.44		2.6	1.44–4.69	<0.01
	UBM	261	27.7%	0.21–0.33		2.11	1.26–3.54	<0.01
	UCB	133	31.5%	0.21–0.40		2.01	1.15-3.26	<0.01
HCT-CI	0–3	548	24.3%	0.20–0.28	0.15	1		
	4–5	43	35.4%	0.16–0.50		1.63	0.86–3.09	0.14
	6-	17	47.6%	0.05–0.71		1.21	0.25–5.71	0.82
Lung infection	Yes	52	25.1%	0.15–0.33	<0.01	2.63	1.53–4.52	<0.01
	No	556	6.3%	0.04–0.09		1		
BI	0≦BI < 500	520	24.2%	0.20–0.28	0.11	1		
	BI≧500	88	33.9%	0.21–0.44		1.04	0.58–1.85	0.9
Variables	**Factors**	**aGVHD[d]**						
		Univariate analysis				**Multivariable analysis**		
		n	**aGVHD**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age	<50	263	40.6%	0.35–0.46	0.45			
	≧50	345	38.1%	0.32–0.44				
Sex	M	347	40.2%	0.35-0.45	0.51			
	F	261	38.6%	0.32–0.44				
Disease risk	Low	432	37.9%	0.33–0.43	0.3			
	High	176	42.9%	0.36–0.49				
Conditioning	MAC	399	37.1%	0.30–0.44	0.22			
	RIC	209	40.9%	0.36–0.46				
HLA	Match	270	38.5%	0.33–0.44	0.04	1		
	Mismatch	168	47.1%	0.38–0.55		1.32	0.95–1.84	0.1
Donor	RBM	128	33.9%	0.25–0.42	0.08	1		
	RPB	86	43.3%	0.31–0.53		1.44	0.92–2.26	0.11
	UBM	261	44.2%	0.38–0.50		1.47	1.01–2.12	0.04
	UCB	133	33.2%	0.24–0.41		0.53	0.06–4.64	0.57
BI	0≦BI < 500	520	40.1%	0.36–0.44	0.47	1		
	BI≧500	88	35.0%	0.24–0.45		0.99	0.64–1.52	0.95
Variables	**Factors**	**cGVHD[e]**						
		Univariate analysis				**Multivariable analysis**		
		n	**5ycGVHD**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age	<50	263	51.0%	0.45–0.57	0.11	1		
	≧50	345	46.5%	0.38-0.53		0.78	0.58–1.04	0.09
Sex	M	347	49.4%	0.42–0.55	0.96			
	F	261	49.9%	0.42–0.56				
Disease risk	Low	432	46.3%	0.40–0.51	0.02	1		
	High	176	58.0%	0.48-0.66		1.3	0.98–1.72	0.09
Conditioning	MAC	399	50.8%	0.44–0.56	0.67			
	RIC	209	46.8%	0.37-0.54				
HLA	Match	270	51.3%	0.44–0.61	0.26	1		
	Mismatch	168	57.4%	0.48-0.63		1.59	1.28–1.98	<0.01
Donor	RBM	128	55.2%	0.44–0.63	<0.01	1		
	RPB	86	52.2%	0.44–0.59		1.04	0.71–1.52	0.85
	UBM	261	63.0%	0.47–0.74		0.82	0.58–1.15	0.25

Table 4. continued

Variables	Factors	OS[a]						
		Univariate analysis				Multivariable analysis		
		n	5yOS	95% CI	*P*	HR	95% CI	*P*
	UCB	133	25.4%	0.11–0.34		0.12	0.05–0.26	<0.01
BI	0 ≦ BI < 500	520	48.5%	0.43–0.53	<0.01	1		
	BI ≧ 500	88	56.9%	0.41–0.68		1.73	1.15–2.61	<0.01

Univariate and multivariable analysis results for overall survival, disease-free survival and cumulative incidence of nonrelapse mortality, aGVHD and cGVHD risk factors in patients after allogeneic bone marrow transplantation.
BI Brinkman index, *M* male, *F* female, *PS* performance status, *HCT-CI* hematopoietic cell transplant-comorbidity index, *RBM* related bone marrow, *RPBSC* related peripheral blood, *UBM* unrelated bone marrow, *UCB* umbilical cord blood, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *HLA* human leukocyte antigen.
[a]For overall survival, hazard ratio is adjusted with recipient age, disease risk, donor source, HCT-CI, and lung infection.
[b]For disease-free survival, hazard ratio is adjusted with recipient age, disease risk, donor source, HCT-CI, and lung infection.
[c]For nonrelapse mortality, hazard ratio is adjusted with recipient age, HLA, donor source, HCT-CI, and lung infection.
[d]For acute GVHD, hazard ratio is adjusted with HLA and donor source.
[e]For chronic GVHD, hazard ratio is adjusted with recipient age, disease risk, HLA and donor source.

Table 5. Characteristics of chronic GVHD.

	0 ≦ BI < 500 *N* (%)	BI ≧ 500 *N* (%)	*p* value
None	328 (63)	54 (61)	0.7
Limited	64 (12)	12 (14)	0.69
Extensive	128 (25)	22 (25)	0.98
Organs involved			
Liver	73 (14)	13 (15)	0.19
Skin	120 (23)	24 (27)	0.04
Mouth	93 (18)	18 (20)	0.08
Eye	64 (12)	11 (13)	0.31
Lung	43 (8)	11 (13)	0.19
Gastrointestinal tract	36 (7)	4 (5)	0.12
Joint	7 (1)	1 (1)	0.24
Therapy			
Steroid	57 (11)	5 (6)	0.13
Cyclosporine	6 (1)	1 (1)	0.99
Steroid + Cyclosporine	12 (2)	2 (2)	0.98
Tacrolimus	6 (1)	1 (1)	0.88
Steroid + Tacrolimus	30 (6)	5 (6)	0.97
Topical only	20 (4)	5 (6)	0.18
Steroid + Lung transplant	1 (1)	0	

Limited and extensive GVHDs are defined according to the Seattle criteria. Where no value is shown, the number of events was too low to calculate a *p* value.

which might have influenced the transplantation outcomes. Patients' willingness to receive HSCT or expectations for HSCT might have led to the under-reporting of smoking history. This bias was more likely to affect the HRs toward the null. In addition, the current study had no strict exclusion criteria based on the PFT results, smoking status, or pulmonary disease for transplantation eligibility at our center. Therefore, patients with severe pulmonary dysfunction or other comorbidities might not have undergone transplantation; thus, a selection bias could have occurred.

In summary, there was a significant association between cigarette smoking and cGVHD after HSCT. Posttransplantation management is important because patients with high BI may be at higher risk for developing cGVHD than those with low BI. The current study highlights the need for further investigations to reveal how smoking leads to higher incidence of cGVHD. Hence, future prospective studies that investigate long-term outcomes of HSCT according to smoking status and continuous monitoring of smoking before and after HSCT must be conducted to explore this notion.

DATA AVAILABILITY

The data supporting the results of this study are available from the corresponding author upon a reasonable request.

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AUTHOR CONTRIBUTIONS

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ETHICAL APPROVAL

This study was performed in accordance with the Declaration of Helsinki and the Ethics Guidelines for Clinical Research published by the Ministry of Health, Labor, and Welfare of Japan. This retrospective study was approved by Ethical Committee for Medical and Biological Research Involving Human Subjects of Yokohama City University Medical Center (B180800006). Approval for the protocol and written informed consent forms were obtained from the ethics committees at each institution. The written decision can be presented upon request.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41409-022-01678-7.

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論文目録

I 主 論 文

Clinical impact of cigarette smoking on the outcomes of allogeneic hematopoietic stem cell transplantation: A multicenter retrospective study

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II 副 論 文

なし

III 参 考 論 文

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