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Late Effects of Allogeneic Hematopoietic Stem Cell Transplantation in an Asian Patient Population

Chong Mui Fong, Lim Yan Jiun, Ng Hong Yen

Department of Pharmacy, Singapore General Hospital, Singapore

Abstract

Background: Long-term survivors of allogeneic hematopoietic stem cell transplantation (alloHSCT) are at a substantial risk of developing medical late effects. We aimed to determine the incidence of metabolic syndrome (MS), cardiovascular (CV) events, bone density loss, and fractures in a cohort of patients who underwent alloHSCT for hematologic disorders. The potential risk factors for MS, CV events, bone density loss, and fractures, as well as the sufficiency of existing monitoring measures in our institution, were also evaluated.

Methods: A single-center, retrospective study was conducted. We included patients who underwent alloHSCT at the Singapore General Hospital between January 2011 and December 2016, were at least 21 years old, and had a minimum follow-up period of 6 months. Patients with MS-related data comprised the CV study population, whereas patients with bone loss-related data comprised the skeletal study population. Associations between risk factors and the development of MS or bone loss were assessed using a univariate analysis followed by multivariate logistic regression. All analyses were performed using SPSS version 23.

Results: A total of 91 patients were included in the CV study population, of which 13 (14.3%) had preexisting MS, 17 (18.7%) developed MS, and 5 (5.5%) developed CV events after alloHSCT. Thirty-one patients were included in the skeletal study population, of which 2 (6.5%) had preexisting bone loss, 23 (71.0%) developed osteopenia or osteoporosis, and 2 (6.5%) had a fracture. After adjusting for preexisting MS, pretransplant abdominal obesity (p=0.002), elevated triglyceride (p<0.001), and fasting hyperglycemia (p<0.001) significantly predicted MS on multivariate analyses. Only female sex predicted the risk of bone loss after alloHSCT on multivariate analyses after adjusting for preexisting osteopenia (p=0.02). Of the 174 patients who underwent alloHSCT during the study period, 83 (47.7%) and 143 (82.2%) patients had no MS-related data and bone loss-related data, respectively.

Conclusion: Long-term alloHSCT survivors are at an increased risk of MS, CV complications, and bone loss. This underscores the importance of close monitoring and timely interventions to reduce long-term morbidity and mortality.

Introduction

Hematopoietic stem cell transplantation (HSCT) is being increasingly used as a potentially curative treatment modality for many high-risk leukemias and non-malignant conditions. However, long-term survivors are at a substantial risk of developing medical late effects[1-4] and face higher mortality rates than the general population[5-7]. In the Bone Marrow Transplant Survivor Study published in 2007, cardiac complications were found to contribute to 3% of premature deaths in bone marrow transplant recipients, and this was increased 2.3-fold compared with the general population[6].

The development of metabolic syndrome (MS) after transplantation is an increasing concern among allogeneic HSCT (alloHSCT) survivors. The prevalence of MS reported in earlier studies conducted among patients from American and European centers ranged from

31-49%[8-12]. In addition to risk factors common to the general population, such as genetic predisposition, age, and lifestyle factors[13], alloHSCT recipients are likely to be more susceptible to MS than the general population for various reasons. These include damage to the neurohormonal system and vascular endothelium from pretransplant conditioning regimen as well as the immunological effects of allografting and development and treatment of graft-versus-host disease (GVHD)[9]. A follow-up study of 23 alloHSCT survivors reported hyperinsulinemia, impaired glucose tolerance, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C) levels, and abdominal obesity to be more common among the alloHSCT survivors as compared with a group of leukemia patients who did not undergo alloHSCT or healthy controls[14].

It has been shown that individuals in the general population with MS are at increased lifetime risk of developing cardiovascular (CV) diseases[15]. As alloHSCT survivors may be at risk of CV diseases secondary to cardiotoxic chemotherapy or radiotherapy[16-18], the presence of MS may increase this risk.

Bone density loss after transplantation is another factor that affects the quality of life of alloHSCT survivors[19]. Resultant fractures result in chronic pain, long-term disability, and premature death[20]. Osteoporosis and osteopenia occur in approximately 32% and 50% of cases, respectively within 6-12 months after alloHSCT[13,19,21-23]. In addition to risk factors common to the general population, alloHSCT-associated risk factors include increased corticosteroid exposure, gonadal insufficiency, and the use of total body irradiation (TBI) as part of conditioning[24,25].

Recommended screening and preventive strategies for HSCT survivors have been made collectively by transplant experts from the European Group for Blood and Marrow Transplantation, Center for International Blood and Marrow Transplant Research, and American Society of Blood and Marrow Transplantation[13,25,26]. However, the applicability of these guidelines in the Asian population is yet to be established. Appropriate population-specific adaptations of these guidelines are required to facilitate the development of screening guidelines and interventions to mitigate CV- and skeletal-related morbidity and mortality among survivors of alloHSCT in the Asian population.

This study aimed to characterize the incidence of MS, CV events, and bone loss in an Asian population who underwent alloHSCT and the factors that predispose them to these long-term complications.

The primary objective of this study was to determine the incidence of MS, CV events, bone density loss, and fractures in a cohort of patients who underwent alloHSCT for hematologic disorders. The secondary objectives were (1) to evaluate the potential association between patient as well as transplant factors and development of MS, CV events, bone density loss, and fractures and (2) to evaluate the sufficiency of existing long-term monitoring strategies.

Materials and Methods

Patients and data management

At the point that this study was conducted, there were no institutional guidelines in place to guide post-transplant follow-up. Primary transplant physicians followed up with patients at regular intervals, and any posttransplant investigations and vaccinations were performed at the discretion of each physician.

Patients aged ≥ 21 years who underwent alloHSCT at Singapore General Hospital between January 2011 and December 2016, with a minimum follow-up period of 6 months, were included in this study. Patients who did not have MS- or bone density loss-related data or had incomplete follow-up were excluded.

A single-center retrospective review was carried out. Patient, transplant, and MS- and bone loss-related variables were collected via review of inpatient and outpatient medical records as well as electronic medication records. All data collected were recorded in a data collection form approved by the Central Institutional Review Board. Informed consent was waived due to the retrospective nature of this study.

Definitions

In this study, MS was defined according to the 2009 International Diabetes Federation and American Heart Association/National Heart, Lung, and Blood Institute criteria[27], by the presence of three or more of its core clinical measures: abdominal obesity, elevated triglyceride (TG) level, reduced HDL-C level, or elevated blood pressure or serum glucose level, as shown in **Table A1** (Appendix). The Asian criteria for abdominal obesity with waist circumference cutoffs of $\geq$90 cm for men and $\geq$80 cm for women were used[15]. A body mass index (BMI) of ≥ 27.5 kg/m^2 was used as a substitute for abdominal obesity if waist circumference was not available[28].

Bone mineral density (BMD) results are expressed as the number of standard deviations from normal values of young, healthy, sex-matched controls (T-score) and from the normal values of age- and sex-matched controls (Z-score). The T-score is generally used to determine BMD in postmenopausal women and men aged ≥ 50 years. For young adults and men up to the age of 49 years, Z-scores are preferred to prevent overestimation of age association of BMD[21,23,29]. Patients were classified according to the World Health Organization defi-

Table 1.   Patient and transplant characteristics by MS status

Characteristic	All patients (n=95)		No MS (n=61)		MS (n=17)		Pre-existing MS (n=13) /		p-value
	N or Median	Percent or Range	n	Percent or Range	n	Percent or Range	n	Percent or Range	
Age, yr	50	21-68	48	21-66	51	27-67	59	38-68	0.003
Race									
Chinese	73	76.8%	47	77.0%	13	76.5%	9	69.2%	
Malay	7	7.4%	6	9.8%	0	0%	1	7.7%	0.300
Others	15	15.8%	8	13.1%	4	23.5%	3	23.1%	
Male gender	41	43.2%	27	44.3%	6	35.3%	8	61.5%	0.351
Primary disease									
Acute leukemia	64	67.4%	40	65.5%	9	53.0%	12	92.3%	
Myelodysplastic syndrome	14	14.7%	9	14.7%	5	29.4%	0	0%	
Chronic leukemia	5	5.3%	4	6.6%	1	5.9%	0	0%	0.543
Lymphoma	6	6.3%	4	6.6%	1	5.9%	1	7.7%	
Others	6	6.3%	4	6.6%	1	5.9%	0	0%	
> 1 HSCT	4	4.2%	3	4.9%	1	5.9%	0	0%	1.00
Stem cell source									
Peripheral blood stem cells	84	88.4%	51	83.6%	16	94.1%	13	100%	
Bone marrow	5	5.3%	4	6.6%	1	5.9%	0	0%	0.595
Cord blood	6	6.3%	6	9.8%	0	0%	0	0%	
Conditioning regimen									
Myeloablative	29	30.5%	23	37.7%	3	17.6%	1	7.7%	0.378
Non-myeloablative / Reduced intensity	66	69.5%	38	62.3%	14	82.4%	12	92.3%	
Use of TBI	30	31.6%	23	37.7%	4	23.5%	2	15.4%	0.238
Immunosuppressant tapering									
Time to immunosuppression tapering, days	99	28-663	97	28-663	103	48-429	90	28-255	0.452
aGVHD Diagnosis	56	58.9%	37	60.7%	10	58.8%	6	46.2%	0.628
aGVHD Treatment									
Budesonide and other topical steroids	40	42.1%	28	45.9%	8	47.1%	3	23.1%	0.297
Systemic steroids	34	35.8%	20	32.8%	7	41.2%	4	30.8%	0.796
cGVHD Diagnosis	40	42.1%	28	45.9%	6	35.3%	4	30.8%	0.505
cGVHD Treatment									
Systemic steroids	33	34.7%	23	37.7%	5	29.4%	3	23.1%	0.605
Total time on systemic steroids, days	84	0-2,061	84	0-1,555	106	0-1,322	34	0-2,061	0.839

MS, metabolic syndrome; HSCT, hematopoietic stem cell transplantation; TBI, total body irradiation; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease

nition[29]. Normal BMD was defined as a T-score ≥ -1 SD, osteopenia was defined as a T-score < -1.0 and > -2.5, and osteoporosis was defined as a T-score ≤ -2.5. Z-scores between -1 and -2 were used to define osteopenia, while Z-scores ≤ -2 were defined as osteoporosis in young adults[22].

CV events included cerebrovascular diseases such as stroke, transient ischemic attack, cerebral arterial occlusion, and symptomatic lacunar infarcts and coronary heart diseases (CHD) such as angina pectoris, myocardial infarction, chronic CHD, and peripheral arterial disease (PAD), which include claudication, rest pain, acute ischemia, and gangrene[18,30].

Statistical analysis

Descriptive statistics were used to summarize the patients' baseline demographics. To compare baseline characteristics between groups, Pearson's chi-square or Fisher's exact test was used for categorical variables, and the Kruskal-Wallis test was used for continuous variables. To study the risk factors associated with the development of MS, patients with preexisting MS and those who developed MS after alloHSCT were grouped together and compared with patients who did not develop MS. This was also performed to investigate the risk factors associated with skeletal events.

Patient and transplant factors that were potentially associated with MS, CV events, and bone loss were assessed using a univariate analysis followed by multivariate logistic regression. Univariate analysis was performed using Pearson's chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. Factors that were found to be clinically and statistically significant ($p<0.05$) during univariate analysis were included in the multivariate analysis. All analyses were performed using SPSS version 23 (Armonk, NY: IBM Corp).

Table 2. Screening recommendations according to current guidelines and screening rates in our study

Organ System	Clinical Measure	Screening recommendations as per current guidelines (13, 25, 26)	This study*
Cardiac and vascular	Weight, height and BMI	- Weight, height and BMI assessment at every clinic visit (at least yearly) - Waist circumference measurement yearly - Consider dual energy X-ray absorptiometry (DXA) to assess sarcopenia	- 100% height and weight at least 6 months post HSCT - Frequency not measured - 0% waist circumference - 0% DXA
	Dyslipidemia	- Initial lipid profile 3 months after HSCT - High-risk patients (on CNIs and corticosteroids), repeat every 3–6 months - Standard risk patients, lipid profile every 5 yrs in males ≥ 35 yo and females ≥ 45 yo - Shorter intervals for lipid levels close to that warranting therapy	- Average number of lipid panel done per patient = 2.8 - Median follow up of 3.6 years (0.53 – 41.3) - Time to first lipid panel not measured - Frequency not measured
	Blood pressure	- Blood pressure assessment at every clinic visit (at least yearly)	- 100% - Measured at each clinic visit - Max 1 year interval between clinic visits
	Hyperglycemia	- High-risk patients with ongoing risk factors (on systemic corticosteroids), HbA1C or fasting plasma glucose (FPG) 3 months after HSCT, repeat every 3–6 months - Standard risk adult patients, screening every 3 years in adults ≥ 45 years or in those with sustained higher blood pressure (>135/80 mmHg)	- 100% FPG at least 6 months post HSCT - Frequency not measured - Time to first FPG not measured - HbA1c not measured
Skeletal	Bone Mineral Density (BMD)	- Dual-photon densitometry (largely superseded by DXA) at 1 year for all alloHSCT recipients - Subsequent testing determined by defects or to assess response to therapy	- Average number of BMD studies done per patient = 0.38 - Median follow up of 4.8 years (1.4 – 6.7)
	Calcium / Vitamin D levels	- No recommendations - Physical activity, vitamin D and calcium supplementation recommended to prevent loss of bone density	- 100% baseline calcium level and 3 (9.7%) baseline vitamin D level checked

*N=91 in CV study population; N=31 in skeletal study population

BMI, body mass index; HSCT, hematopoietic stem cell transplantation; CNIs, calcineurin inhibitors; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; DEXA, dual-energy x-ray absorptiometry

Results

Patient and transplant characteristics

A total of 174 patients met the inclusion criteria. However, 79 patients that did not have both MS- and bone loss-related data and were excluded. Of the remaining 95 patients included, four did not have any MS-related data, and 64 did not have any bone loss-related data. Hence, 91 patients comprised the CV study population, and 31 patients comprised the skeletal study population. The patient and transplant characteristics are summarized in **Table 1**.

The median age of the study population was 50 (range, 21-68) years, and 41 (43.2%) of them were men. Seventy-three patients (76.8%) were Chinese, and the majority (67.4%) received alloHSCT for acute leukemia. Twenty-nine patients (30.5%) received myeloablative conditioning, and 30 patients (31.6%) received a conditioning regimen that included the use of TBI.

The median age of the 31 patients included in the skeletal study population was 48 (range, 27-68) years. The median BMI was 21.5 (range, 16.2-34.2) kg/m². Four patients (12.9%) were men, and the majority were Chinese (77.4%). There were no differences between the groups at baseline when categorized according to

bone loss status.

When patients were categorized based on no development of MS, MS developed after HSCT and preexisting MS, only age was significantly different between the three groups. Patients with preexisting MS and those who developed MS after alloHSCT were older than those who did not develop MS (median age, 59, 51, and 48 years, respectively; p=0.005). The use of TBI as part of conditioning and diagnoses of acute and chronic GVHD were not different between the groups. **Table 2** illustrates the frequency of screening for each clinical measure in the study population, as compared with currently published recommendations[13,25,26].

Incidence of MS and CV events in the CV study population

Of the 91 patients, 17 (18.7%) developed MS after alloHSCT. Together with the 13 patients (14.3%) with preexisting MS, the prevalence of MS was 33%, with a median follow-up of 3.6 (range, 0.53-41.3) years. The median time to diagnosis of MS was 356 (range, 44-1,792) days after alloHSCT. Five patients (5.5%) developed CV events, all of whom had CHD. Four of the CV events occurred in patients without MS, and one occurred in a patient with preexisting MS (**Figure 1**).

Incidence of bone loss and fractures in the skeletal study population

Of the 31 patients in the skeletal study population, 12 (38.7%) developed osteopenia after alloHSCT, and 11 (35.5%) developed osteoporosis, with a median follow-up of 4.8 (range, 1.4-6.7) years. Two patients (6.5%) had preexisting osteopenia, one of whom developed osteoporosis after alloHSCT but did not suffer any fractures. The total prevalence of bone loss in the study population was 80.7%. Two patients (6.5%) developed fractures after transplantation. Both fractures were nonvertebral fractures. One of the patients who suffered a fracture had preexisting osteopenia, while the other developed osteoporosis after alloHSCT. The results are summarized in **Figure 2**. Only 13 (41.9%) patients in the skeletal study population received calcium and vitamin D supplementation after alloHSCT. Only one patient who received supplementation had a fracture.

Risk factors for MS

Table 3 summarizes the risk factors associated with MS from the univariate and multivariate analyses. From the univariate analysis, the risk factors identified in-

Figure 1. Incidence of MS and CV events
CV event in groups with No MS, MS and preexisting MS
CV, cardiovascular; MS, metabolic syndrome

cluded old age (p=0.003), baseline abdominal obesity (Odds Ratio [OR], 25.7; 95% Confidence Interval [CI], 3.1-215.3), elevated TG level (OR, 9.2; 95% CI, 3.0-27.7), reduced HDL-C level (OR, 3.9; 95% CI, 1.4-10.7), hypertension (HTN) (OR, 12.0; 95% CI, 4.0-36.4), and fasting hyperglycemia (OR, 22.6; 95% CI, 14.6-110.0). However, the factors that remained significant from the multivariate analysis, adjusted for preexisting MS, were baseline abdominal obesity (OR, 45.5; 95% CI, 4.0-500), elevated TG level (OR, 16.4; 95% CI, 3.8-71.4), and fasting hyperglycemia (OR, 43.5; 95% CI, 6.8-250). Other factors such as calcineurin inhibitor use, corticosteroid use, use of TBI in conditioning, time to immunosuppressant tapering, and GVHD status were not significantly different between the groups. Risk factors for CV events have not been studied because of the low incidence rate.

MS and related clinical measures

Analyzing the three groups separately, it was observed that, in addition to reduced HDL-C level, the incidence of each pretransplant clinical measure meeting the criteria for MS was highest among patients with preexisting MS and lowest in patients who did not develop MS. In addition, regardless of MS status, the incidences of abdominal obesity, elevated TG level, reduced HDL-C level, HTN, and elevated fasting glucose levels were higher after transplantation in all three groups. Of the five clinical measures of MS, dyslipidemia after alloHSCT was the most common. A total of 62 (68.1%) patients had elevated TG levels, and 48 (52.7%) had reduced HDL-C levels after alloHSCT. The results are summarized in **Table 4**.
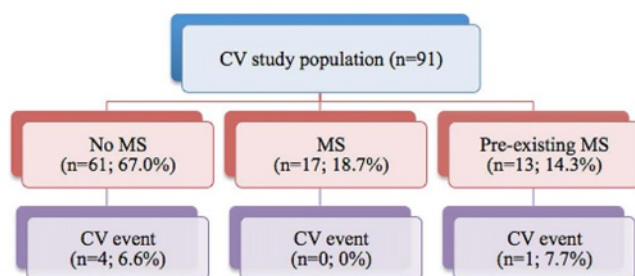
Risk factors for bone loss

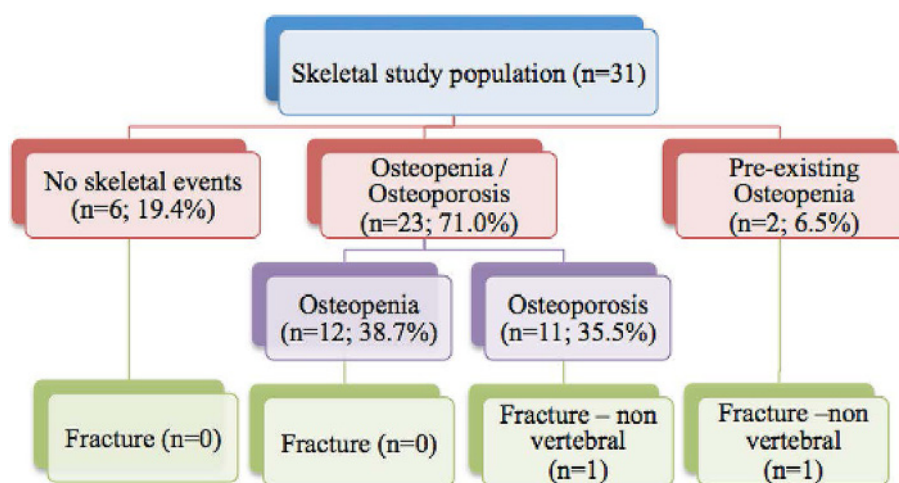Risk factors associated with bone loss from the uni-

Figure 2. Incidence of bone loss and fractures
Fracture in groups with no bone loss, bone loss and preexisting bone loss

Table 3. Univariate and multivariate analysis for risk factors predictive of MS (N=91)

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	NA	0.003	NA	NA
Abdominal obesity	25.7 (3.1 – 215.3)	<0.001	45.5 (4.0 – 500.0)	0.002
Elevated triglycerides	9.2 (3.0 – 27.7)	<0.001	16.4 (3.8 – 71.4)	<0.001
Reduced HDL-C	3.9 (1.4 – 10.7)	0.007	NA	NA
Hypertension	12.0 (4.0 – 36.4)	<0.001	NA	NA
Fasting hyperglycemia	22.6 (14.6 – 110.0)	<0.001	43.5 (6.8 – 250.0)	<0.001

MS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol

Table 4. Incidences of clinical measures of MS by MS status

n (%)	Pre (A)*	Post (A)	Pre (B)*	Post (B)	Pre (C)*	Post (C)	Pre (Total)	Post (Total)
Abdominal Obesity	1 (1.6)	5 (8.2)	4 (23.5)	6 (35.3)	5 (38.5)	8 (61.5)	10 (11.0)	19 (20.9)
Elevated TG	6 (9.8)	35 (57.4)	6 (35.3)	15 (88.2)	9 (69.2)	12 (92.3)	21 (23.1)	62 (68.1)
Reduced HDL-C	9 (14.8)	23 (37.7)	1 (5.9)	13 (76.5)	11 (84.6)	12 (92.3)	21 (23.1)	48 (52.7)
HTN	6 (9.8)	12 (19.7)	5 (29.4)	11 (64.7)	12 (92.3)	12 (92.3)	23 (25.3)	35 (38.5)
Elevated FG	2 (3.3)	6 (9.8)	4 (23.5)	13 (76.5)	9 (69.2)	9 (69.2)	15 (16.5)	28 (30.8)

 (A): Patients without post HSCT MS,

 (B): Patients with post HSCT MS,

 (C): Patients with pre-existing MS

 * Statistical significance between groups for all clinical measures (p<0.001)

 TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; FG, fasting glucose; HSCT, hematopoietic stem cell transplantation; MS, metabolic syndrome

Table 5. Univariate and multivariate analysis for risk factors predictive of bone loss (N=31)

Variables	Univariate Analysis		Multivariate Analysis (Adjusted for pre-existing osteopenia)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Female	17.3 (1.4 – 210.1)	0.028	50 (1.9 – 1,000)	0.02
Baseline BMI	NA	0.038	1.9 (1.0 – 3.6)	0.06

BMI, body mass index

variate and multivariate analyses are summarized in **Table 5**. The univariate analysis identified female sex (OR, 17.3; 95% CI, 1.4-210.1) and baseline BMI (p= 0.038) as risk factors for bone loss. The median baseline BMI for patients who developed bone loss was 21.3 (range, 16.2-26.7) kg/m^2, while that for patients who did not develop bone loss was 24.3 (range, 21.3-34.2) kg/m^2. Female sex remained significant in the multivariate analysis after adjusting for preexisting osteopenia (OR, 50; 95% CI, 1.9-1,000). Other factors such as calcineurin inhibitor use, corticosteroid use, time to immunosuppressant tapering, and GVHD status were not significantly different between the two groups. Risk factors for fractures have not been studied because of the low incidence rate.

Sufficiency of current screening measures

Among the 174 patients who met the study's inclu-sion criteria, 79 did not have both MS- and bone loss-related data. Another 95 patients did not have MS- or bone loss-related data. This resulted in a total of 83 patients (47.7%) without MS-related data and 143 patients (82.2%) without bone-related data. All patients who were not included due to incomplete MS-related data did not have lipid panel results. Similarly, none of the patients excluded from the skeletal event analysis had BMD measurements.

In the CV study population, none of the patients had their waist circumference measured. However, all of the patients included had their height and weight monitored. An average of 2.8 lipid panels per patient were performed, at a median follow-up of 3.6 (range, 0.53-41.3) years. All included patients had sufficient blood pressure and glucose monitoring. In the skeletal study population, an average of 0.38 BMD studies were performed per patient.

Discussion

The incidence of MS in this study was 18.7%, similar to that reported in other studies, as summarized in **Table A2** (Appendix), ranging from 17-48%[11,12]. The study by Oudin et al.[12] reported a low incidence of 17%, likely due to the inclusion of both autologous HSCT and alloHSCT survivors. The median time to diagnosis of MS in this study was 356 (range, 44-1,792) days, with a median follow-up of 3.6 (range, 0.53-41.3) years. This was similarly reported in an earlier study where MS occurred as early as 1 year after alloHSCT[11], although other studies reported the occurrence of MS at a median of 4-15 years after alloHSCT[8,9,31]. The prevalence of MS in this study was 33%, which is in concordance with previous studies. For adolescent survivors, the prevalence of MS varied from 7-32%[10,14,32-35] at a median of 4-15 years after HSCT. In adults, it ranged from 29-49% at a median of 3-9 years after HSCT among mixed cohorts of adult autologous and allogeneic HSCT survivors[8,9,31]. The prevalence of MS in this study was also higher than that of the general population of Singapore, which was reported to range from 20.0-26.9% depending on the criteria used to define MS[36].

Baseline abdominal obesity, elevated TG level, and fasting hyperglycemia were significant in the multivariate analysis adjusted for preexisting MS. This is an important finding as it underscores the importance of controlling risk factors before transplantation to optimize outcomes after alloHSCT.

Although the use of corticosteroids and calcineurin inhibitors as part of GVHD prophylaxis and treatment is known to cause metabolic derangements, such as hyperglycemia and HTN and has been previously reported to increase the risk of MS[10], such findings were not reproduced in this study. This could potentially be due to differences in genetic disposition and ethnicity among the different study populations. Total time on systemic steroids, time to immunosuppressant tapering, and diagnosis of GVHD were not significantly different between the groups, according to MS status, similar to findings by other groups[9,11].

Earlier studies have suggested that the use of TBI may contribute to the premature development of MS components[11,12,37]. In this study, however, TBI was not shown to be a significant risk factor for MS. This could be related to the relatively lower percentage of patients treated with TBI in this study (31.6% vs. 48-73%).

Regardless of MS status, all clinical measures of MS were significantly higher after HSCT than at baseline. Similar results were reported in earlier studies, which showed that alloHSCT increased the risk of developing abdominal obesity, dyslipidemia, HTN, and diabetes[10,30,38-41].

Dyslipidemia was noted to be the most common clinical measure of MS in patients after HSCT. The incidences of reduced HDL-C and elevated TG levels were 78.7% and 68.1%, respectively. Elevated TG levels were also commonly identified in other studies that included mostly older adults[8,9,11,31]. Another study that included young adults revealed a low HDL level to be the most common component[10]. This finding emphasizes the importance of routine monitoring of lipid panels in this patient population, given that dyslipidemia is common following HSCT[8,9,11,31].

Waist measurements were not available for all patients, and BMI was used as a substitute. The use of BMI as a clinical measure of MS in this patient population may not be ideal, considering that many studies report the observation of normal BMI despite the prevalence of other metabolic disturbances[42,43]. This was attributed to the development of significantly altered body composition in posttransplant patients, where sarcopenic obesity resulted in an increase in the total percentage of fat mass and a decrease in lean body mass. These patients may develop insulin resistance due to the loss of myocyte insulin receptors and an increase in adipocyte insulin receptors, which are less efficient in binding insulin and clearing glucose[43].

The incidences of osteopenia and osteoporosis were determined to be 38.7% and 35.5%, respectively, in this study, comparable to those reported in similar studies that revealed osteopenia rates between 42% and 50% and osteoporosis rates between 25% and 32%[13,19,21-23]. However, the rate of osteoporosis in this study was higher than that reported in the general population of Singapore. In a study conducted in community-dwelling adults in Singapore, the prevalence of osteoporosis was reported to be 9.3% and 0.7% in women and men, respectively. On the other hand, the rate of osteopenia was similar to that in this study. The prevalence was reported to be 23.1% and 48.8% in women and men, respectively[44].

Female sex was identified as a risk factor for the development of bone loss after alloHSCT from the multivariate analysis after adjusting for preexisting osteopenia. This was also observed in previous studies[13]. Female sex is also a common risk factor for bone loss in the general population[45], and the HSCT process could potentially exacerbate the risk in this group of patients.

Prior studies have shown that the use of corticosteroids and calcineurin inhibitors may accelerate bone loss in alloHSCT recipients by decreasing bone production and increasing bone resorption[21,46,47]. In this study, however, this association was not identified, which is consistent with the findings of three other studies[19,48,49]. It is postulated that mechanisms other than corticosteroid and calcineurin inhibitor use may contribute to BMD

loss after alloHSCT. This may be a result of direct toxicity to the bone and bone marrow stromal cells by conditioning as well as bone loss promoted by rapid changes in cytokines immediately following HSCT[19].

It was found that the current recommendations were not adhered to for several important parameters. Almost half of the study population (47.7%) did not have their lipid panels measured. According to current guideline recommendations[13,26], all patients should have an initial lipid profile performed 3 months after HSCT, followed by regular intervals according to their risk category. Nonadherence was likely due to a lack of available institutional guidelines. This is an exceptionally important finding and area for improvement, as it is evident from the results that this patient population is especially susceptible to dyslipidemia after alloHSCT. Although the correlation between poorly controlled CV risk factors and CV events was not demonstrated in this study due to the small number of events, it is an established fact that dyslipidemia may potentially contribute to increased CV morbidity and mortality in the long run[50,51].

Deficiency in bone loss screening was also found in this study, where 82.2% of the patients did not have BMD data available at a median follow-up of 4.8 years. The incidences of bone, loss, and fractures in Asia are similar or even higher than those in Western countries due to widespread calcium and vitamin D deficiency, even in the general population[52]. The rate of calcium and vitamin D supplementation in this study population was also low (41.9%). Taken together, these findings underscore the importance of implementing measures to ensure routine and timely screening for bone loss and calcium/vitamin D deficiency after HSCT.

The limitations of this study include its retrospective nature, and only associations, but not causal relationships, could be determined. Furthermore, the accuracy and completeness of the data collection were largely dependent on high-quality existing data. The small sample size and heterogeneity of patients were other limitations that would warrant further studies in other independent cohorts to confirm the results of this study. The small sample size of this study also contributed to the inability to identify risk factors for CV events and fractures.

Due to the lack of data in many patients, selection bias could not be excluded. Patients deemed to be at higher risk of posttransplant complications might have been screened and followed up more closely. Confounding factors such as dietary patterns, alcohol intake, smoking status, and other lifestyle modifications as well as family history of CV diseases were not adequately captured in this study. We also did not examine the previous chemotherapy history of these patients, particularly the use of anthracyclines, which have been well established, to contribute to late CV complications.

Future directions and conclusion

Currently, there are no institutional guidelines recommending the initial and subsequent screening time points. This study outlines the importance of developing institutional guidelines and implementation methods to improve long-term outcomes. This could be performed by implementing a screening chart for physicians to follow up on tests that are required at each time point or setting up a long-term follow-up clinic, where specialized physicians and healthcare professionals work together to monitor these survivors to ensure optimal long-term outcomes.

In conclusion, this study showed that suboptimal control of CV risk factors at baseline may potentially increase the risk of developing MS after alloHSCT. Females are also at an increased risk of developing bone loss after alloHSCT. This highlights the importance of screening for all clinical measures of MS and identifying patients at risk of bone loss prior to transplantation, as well as frequent monitoring in these patients after HSCT. Strategies to ensure timely and adequate monitoring and preventive measures are crucial.

However, with the limitations of a short study duration and small number of events, the risk factors for CV events and fractures could not be fully elucidated. More studies with longer follow-up periods are needed to fully understand the long-term implications of MS and bone loss in patients after alloHSCT.

Author Contributions

M.F. Chong designed the study, collected and analyzed data, and wrote the manuscript.

Y.J. Lim and H.Y. Ng provided guidance on the above.

Conflicts of Interest

The authors declare no conflict of interest. Disclosure forms provided by the authors are available on the website.

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