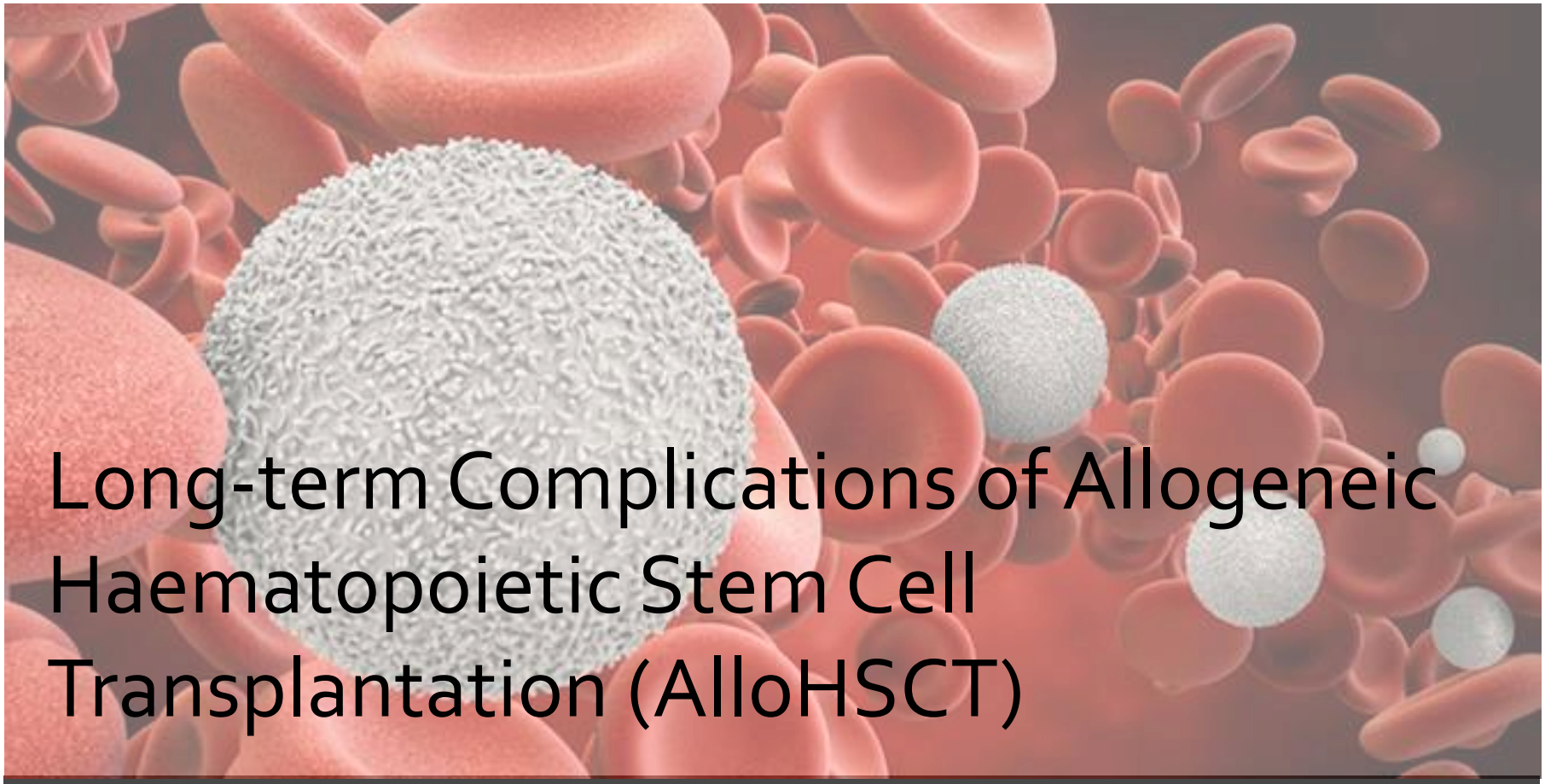


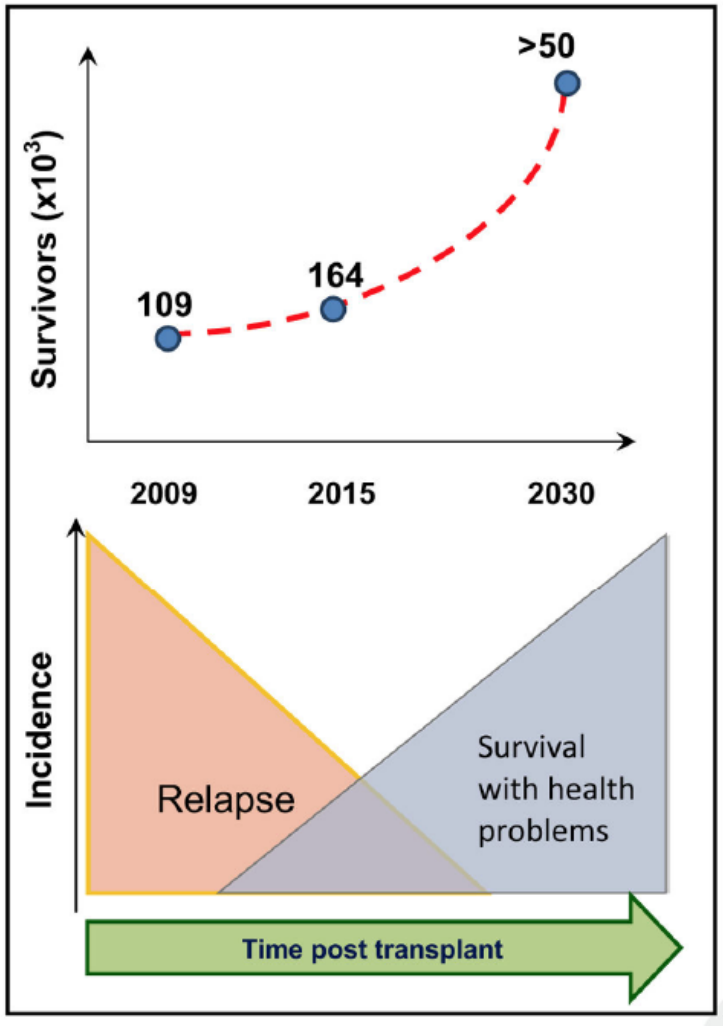
Long-term Complications of Allogeneic Haematopoietic Stem Cell Transplantation (AlloHSCT)

Chong Mui Fong, Pharm.D., BCPS, BCOP
Senior Clinical Pharmacist
Singapore General Hospital
9 September 2018

Objectives

- To describe the burden of morbidity experienced by alloHSCT survivors
- To identify populations at increased risk of long term complications experienced by alloHSCT survivors
- To summarize current follow-up recommendations for long-term survivors of alloHSCT

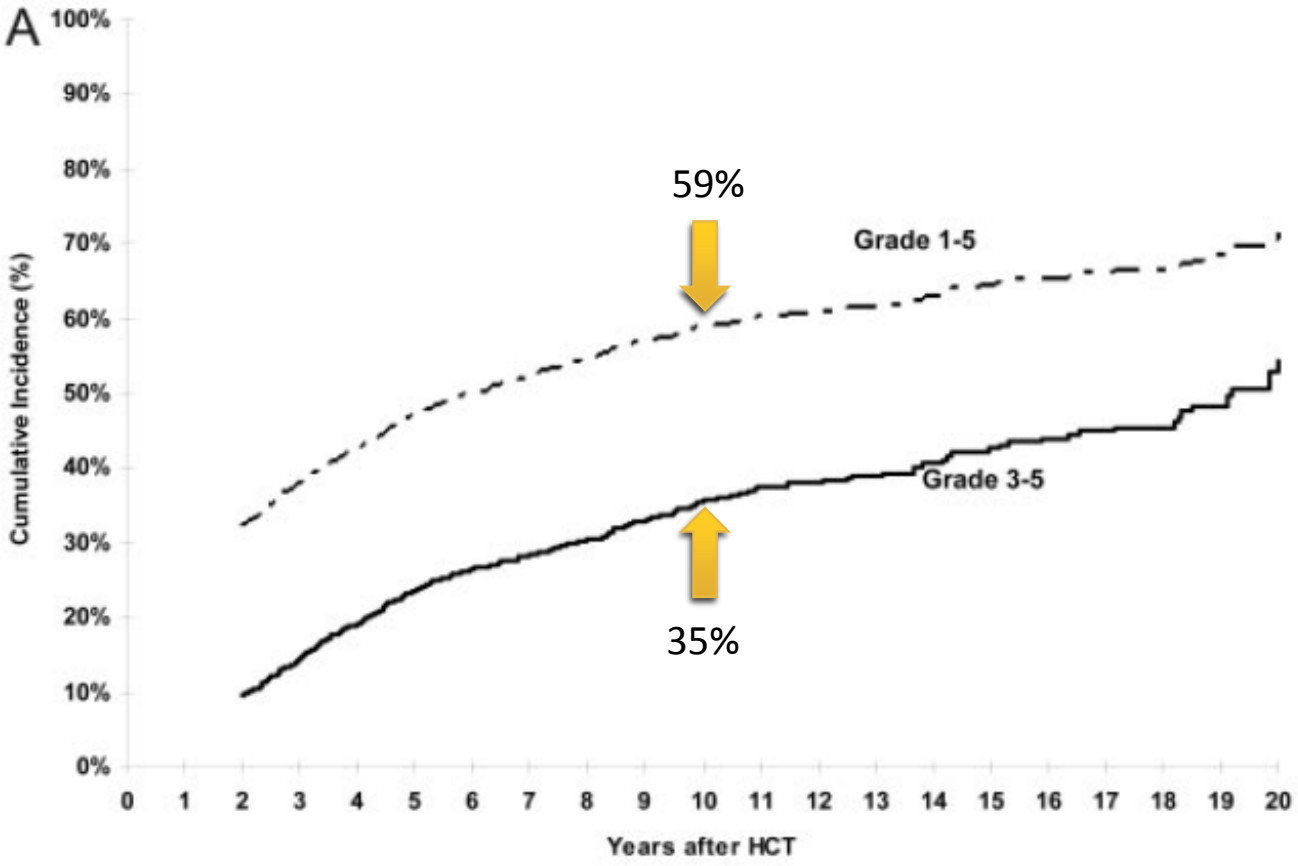
Projected numbers of HSCT survivors and temporal course after HCT



- HCT survivors continue to remain at risk for late effects long after the risk of malignancy relapse has abated

Battiwalla et al. Biol Blood Marrow Transplant. 2017 ; 23(2): 184–192.

HSCT survivors have higher risk of chronic health problems compared to siblings



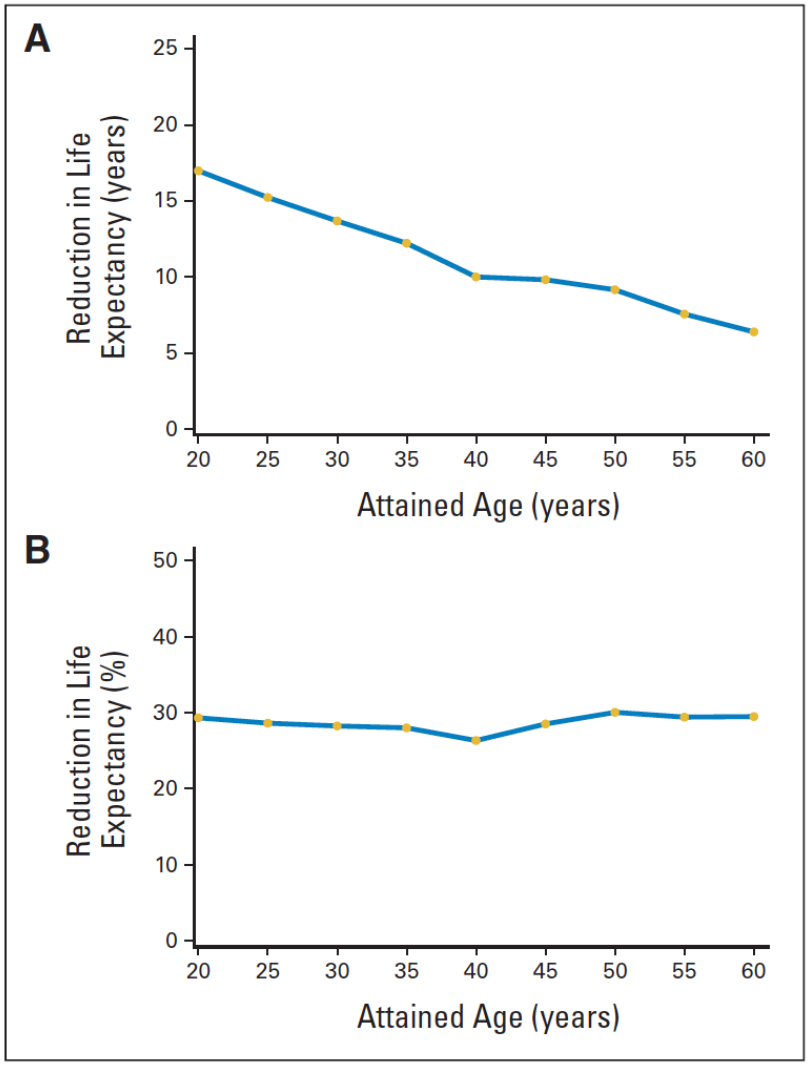
Relative risk (RR) compared to siblings

Chronic problems	RR	95% CI
Overall	1.81	1.55 – 2.11
Grade 3-5	3.52	2.31 – 5.38

HSCT survivors: 3.5 fold risk of severe / life-threatening conditions compared to siblings

Sun CL et al. Blood. 2010;116(17):3129-39

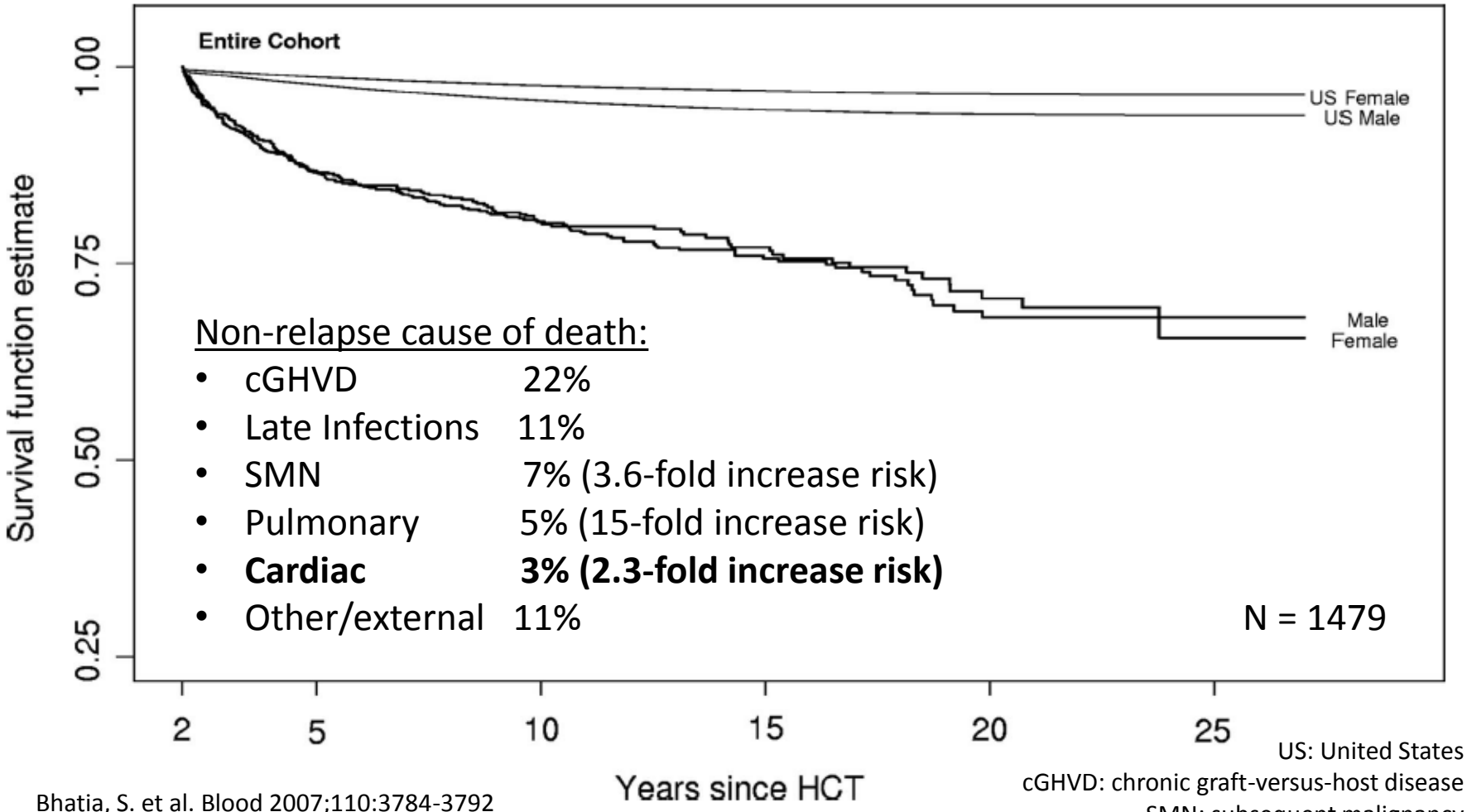
Projected Reduction in Life Expectancy Relative to US Population Data as a Function of Attained Age



- The absolute decrease in estimated residual life expectancy ranges from 17.0 years for survivors at 20 years of age to 6.4 years for survivors at 60 years of age
- The proportionate reduction in life expectancy is approximately 30% at any attained age

Martin PJ, et al. J Clin Oncol 2010;28:1011-1016

Late Mortality >2 years after HSCT



Non-relapse cause of death:

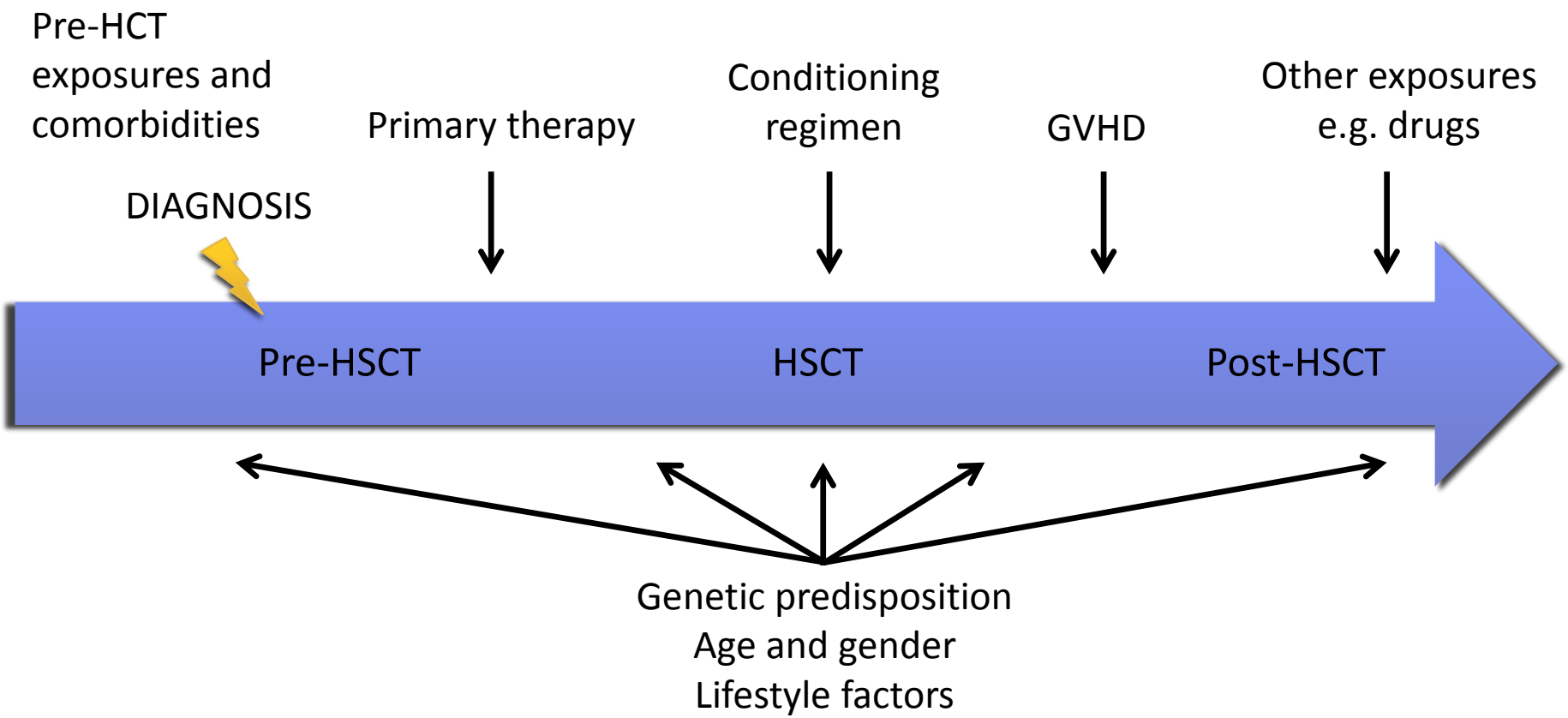
- cGHVD 22%
- Late Infections 11%
- SMN 7% (3.6-fold increase risk)
- Pulmonary 5% (15-fold increase risk)
- **Cardiac 3% (2.3-fold increase risk)**
- Other/external 11%

N = 1479

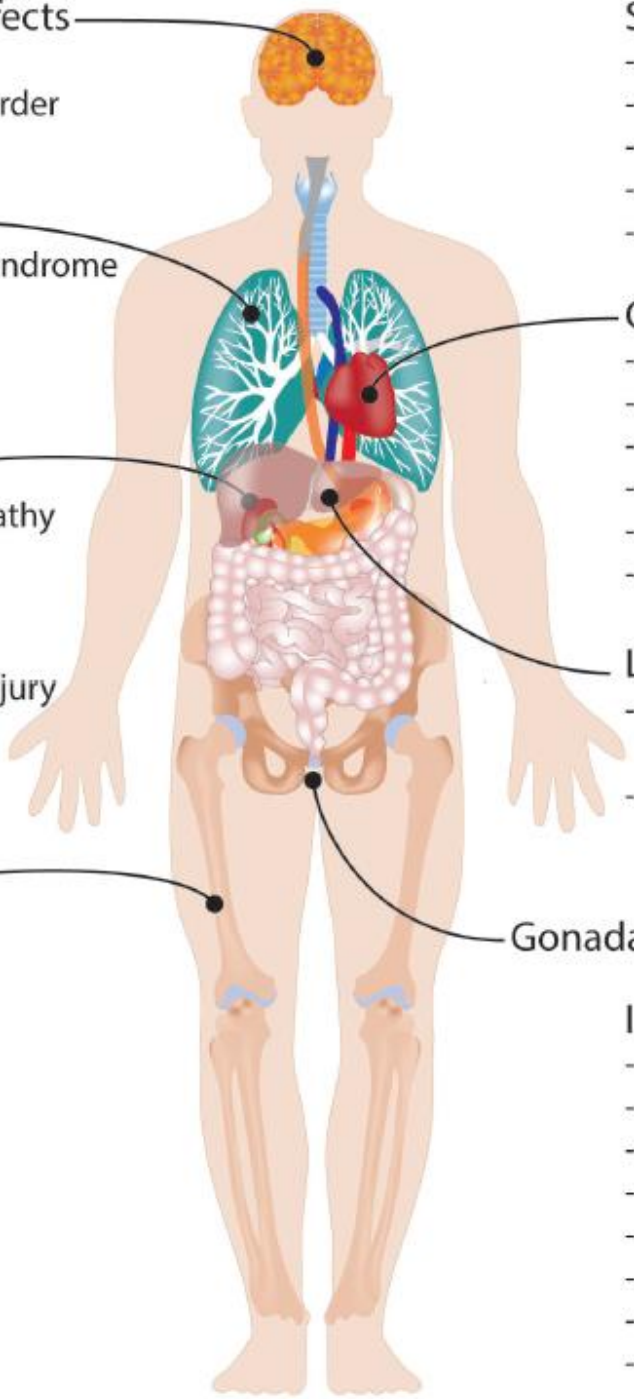
Bhatia, S. et al. Blood 2007;110:3784-3792

US: United States
cGHVD: chronic graft-versus-host disease
SMN: subsequent malignancy

Risk Factors for Late Complications



Majhail NS et al. Biol Blood Marrow Transplant. 2012 Mar;18(3):348-71.
Wingard JR, Gastineau DA, Leather HL, Snyder E, Szczepiorkowski ZM, eds. Hematopoietic Stem Cell Transplantation: A Handbook for Clinicians. Bethesda, MD: American Association of Blood Banks (AABB). 2009:473-484.



Neuropsychological effects
- Depression, anxiety
- Post-traumatic stress disorder
- Neurocognitive deficits

Pulmonary diseases
- Bronchiolitis obliterans syndrome
- Cryptogenic organizing pneumonia
- Pulmonary hypertension

Kidney diseases
- Thrombotic microangiopathy
- Nephrotic syndrome
- Idiopathic chronic kidney disease
- Persistent acute kidney injury
- BK virus nephropathy

Iron overload

Bone diseases
- Osteopenia
- Osteoporosis
- Avascular necrosis

Endocrine diseases
- Thyroid dysfunction
- Gonadal dysfunction
- Diabetes
- Dyslipidemia
- Metabolic syndrome
- Adrenal insufficiency

Solid cancer
- Oral cavity
- Skin
- Breast
- Thyroid
- Other sites

Cardiovascular diseases
- Cardiomyopathy
- Congestive heart failure
- Valvar dysfunction
- Arrhythmia
- Pericarditis
- Coronary artery disease

Liver diseases
- Hepatitis B, Hepatitis C, liver cirrhosis
- Nodular regenerative/focal nodular hyperplasia

Gonadal dysfunction/infertility

Infectious diseases
- *Pneumocystis jirovecci*
- Encapsulated bacteria
- Fungi
- Varicella-zoster virus
- Cytomegalovirus
- Respiratory syncytial virus
- Influenza virus
- Parainfluenza virus

Inamoto Y et al. Haematologica. 2017;102(4):614-625.

Table 1. Late effects after blood and marrow transplantation

Late effect	Incidence	Mortality	Morbidity	Treatable	Preventable
Cardiovascular	+	+	+	+	+
Pulmonary					
Bronchiolitis obliterans syndrome	+	++	++	+	-
Cryptogenic organizing pneumonia	+	+	+	++	-
Pulmonary hypertension	+	++	++	+	-
Endocrine					
Thyroid dysfunction	++	-	-/+	+++	-
Diabetes	++	+	+	+++	-
Dyslipidemia	++	-	-/+	+++	-
Adrenal insufficiency	+	-	-/+	+++	-/+
Gonadal dysfunction/ infertility	+++	-	-	-/+	-/+
Iron overload	++	-	-	++	-
Liver					
Hepatitis B	+	-	+	++	+
Hepatitis C and cirrhosis	+	-	+	++	-/+
Nodular regenerative hyperplasia	+	-	-	-	-
Focal nodular hyperplasia	+	-	-	-	-
Kidney					
Thrombotic microangiopathy	+	+	++	-/+	-
Nephrotic syndrome	+	-	++	++	-
Idiopathic chronic kidney disease	+	-	++	+	-
Bone					
Osteoporosis/osteopenia	++	-	-	++	+
Avascular necrosis	+	-	++	++	-
Infection	++	+	+	+++	+
Solid cancer	+	++	+++	-/+	-
Neuropsychological	++	-	++	+	-
Recurrent disease	++	+++	+++	-/+	-
Chronic graft-*versus*-host disease	++	+	++	+	-

+ : <20%; ++ : 20%-50%; +++ : >50%.

Inamoto Y et al. Haematologica. 2017;102(4):614-625.

Metabolic Syndrome and Cardiovascular Disease

Table 1. Definitions of metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII), the International Diabetes Federation (IDF), the American Heart Association (AHA) and the World Health Organization (WHO)

	WHO 1998	*NCEP ATPIII 2005*	*IDF/AHA 2009*
Definition	DM/IFG or IGT or IR plus ⩾2 risk factors	⩾3 risk factors	⩾3 risk factors
Risk factor			
Abdominal obesity	Waist circumference: dependent on ethnicity	Waist circumference: >102 cm (>40 in) in men; >88 cm (>35 in) in women	Waist circumference: population- and country-specific definitions
Triglycerides	⩾150 mg/dL (⩾1.7 mmol/L)	⩾150 mg/dL (⩾1.7 mmol/L) or drug treatment for elevated levels	⩾150 mg/dL (⩾1.7 mmol/L) or drug treatment for elevated levels
HDL cholesterol			
Men	<35 mg/dL (0.9 mmol/L)	<40 mg/dL (<1.0 mmol/L) or drug treatment for reduced levels	<40 mg/dL(<1.0 mmol/L) or drug treatment for reduced levels
Women	<39 mg/dL (1.0 mmol/L)	<50 mg/dL (<1.3 mmol/L) or drug treatment for reduced levels	<50 mg/dL (<1.3 mmol/L) or drug treatment for reduced levels
Blood pressure	⩾140/⩾90 mm Hg	⩾130/⩾85 mm Hg or drug treatment for HTN	⩾130/⩾85 mm Hg or drug treatment for HTN
Fasting glucose	IGT, IFG, or type 2 DM	⩾100 mg/dL (⩾6.11 mmol/L) or drug treatment for DM	⩾100 mg/dL (⩾5.6 mmol/L) or drug treatment for DM
Microalbuminuria	>30 mg albumin per g creatinine		

Abbreviations: DM = diabetes mellitus; HDL = high-density lipoprotein cholesterol; HTN = hypertension; IGT = impaired glucose tolerance (2-h postprandial glucose 140–199 mg/dL (7.8–11.1 mmol/L)); IFG = impaired fasting glucose (fasting glucose 100–126 mg/dL (5.6–7 mmol/L)); IR = insulin resistance.

DeFilipp Z et al. Bone Marrow Transplant. 2017;52(2):173-82.

Metabolic Syndrome and Cardiovascular Disease

- Prevalence varies from 7.5 – 49%
- Occurs at median of 4 to 18 years after HSCT
  - McMillen et al. reported 40% of adult alloHSCT population with MS at 1 year
  - Longer follow up data not included to show if persisted over time

Turcotte LM et al. Biol Blood Marrow Transplant. 2016;22(7):1159-66.

Metabolic Syndrome and Cardiovascular Disease

- AlloHCT recipients predisposed to develop MS through several mechanisms
  - Conditioning regimen-mediated damage to the neurohormonal system and vascular endothelium e.g. TBI
  - Immunological and inflammatory effects of allografting
  - Subsequent GvHD and its therapy

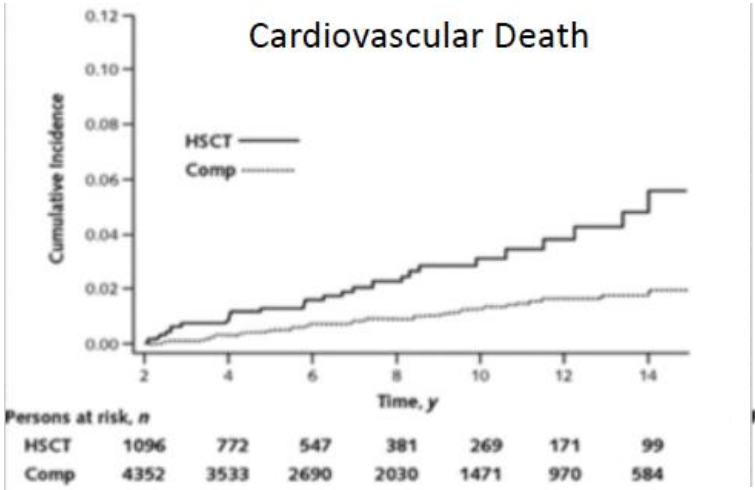
DeFilipp Z et al. Bone Marrow Transplant. 2017;52(2):173-82.

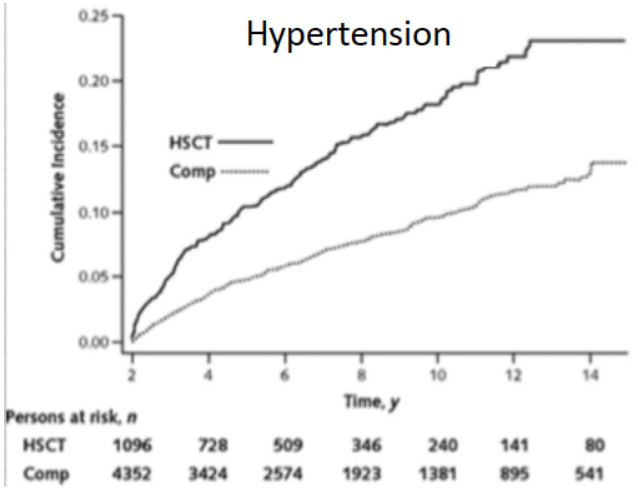
Metabolic Syndrome and Cardiovascular Disease

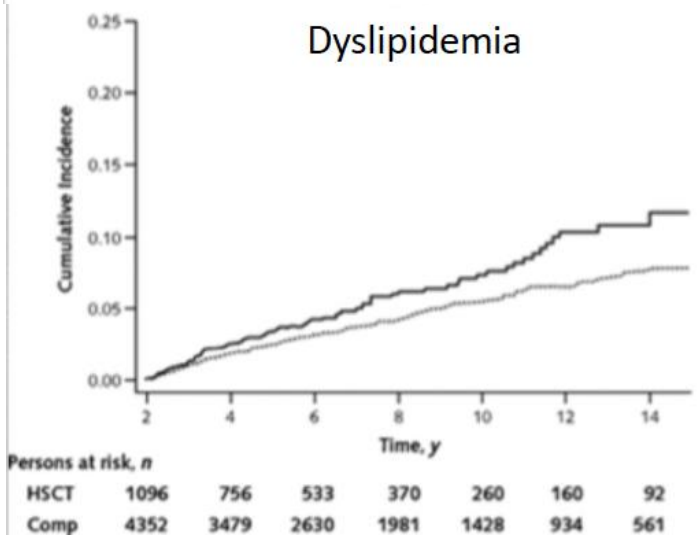
- MS has not yet been proven to impact cardiovascular risk after alloHSCT
- Individuals in the general population with MS twice as likely to develop CV disease than those without MS

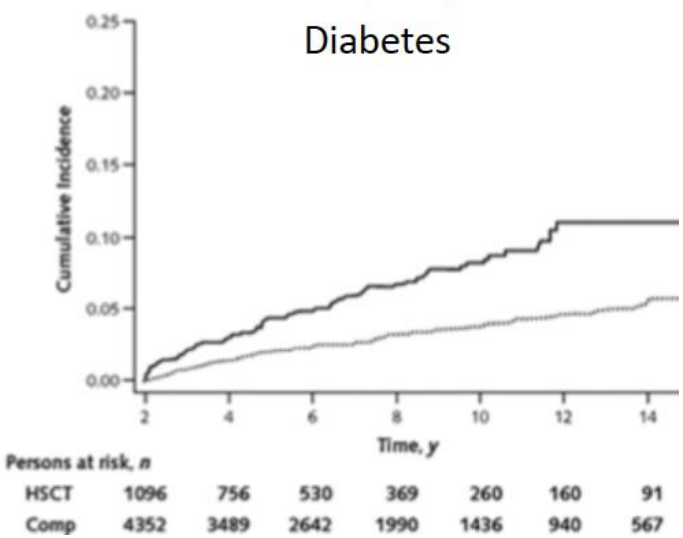
DeFilipp Z et al. Bone Marrow Transplant. 2017;52(2):173-82.
Grundy SM et al. Circulation. 2005;112(17):2735-52.

Cardiovascular Death Among Recipients of HSCT









Risk of cardiovascular hospitalizations and mortality increased by 3.6-fold in HSCT recipients compared with the general population

Chow EJ, et al. Ann Intern Med. 2011;155(1):21-32.

Monitoring Recommendations

Organ system	Clinical measure	Screening guidelines - 2017 CIBMTR and EBMT, 2012 CIBMTR and NMDP recommendations
Cardiac and vascular	Weight, height and BMI	- Weight, height and BMI assessment at every clinic visit (at least yearly) - Waist circumference measurement yearly - Consider DXA to assess sarcopenia
	Dyslipid-emia	- 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
	Blood pressure	- Blood pressure assessment at every clinic visit (at least yearly)
	Hyper-glycemia	- High-risk patients with ongoing risk factors (on systemic corticosteroids), HbA1C or fasting plasma glucose 3 months after HCT, 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)

DeFilipp Z et al. Bone Marrow Transplant. 2017;52(2):173-182.

Bone Diseases

- Bone loss
  - Osteopenia – T score between -1 and -2.5
  - Osteoporosis – T score ≤ -2.5
- Incidence has been reported up to 32% for osteoporosis and 50% for osteopenia with occurrence within 6-12 months after alloHSCT
  - Most significant loss in BMD during first 6 months after HSCT

Cosman F et al. Osteoporos Int. 2014;25(10):2359-81.
NS Majhail et al. Bone Marrow Transplant. 2012;47(3):337-41.
Bhatia S. Hematology Am Soc Hematol Educ Program. 2014 ;2014(1):495-503.

Mechanisms of Bone Loss

Contributing factor	*Mechanism*
Increase in bone resorption	
Renal dysfunction	Decrease in 1,25 $(OH)_2$ vitamin D3 production, secondary hyperparathyroidism
Calcineurin inhibitors	Decrease in renal function, osteoclast activation
Chemotherapy	Hypogonadism causing decrease in estrogen and testosterone
TBI/cranio-spinal irradiation	Hypogonadism
Corticosteroids	Osteoclast activation, secondary hyperparathyroidism
Decrease in bone production	
Malabsorption (e.g. GVHD, mucositis)	Decrease in calcium and vitamin D absorption
Renal dysfunction	Magnesium and calcium wasting
Chemotherapy	Direct inhibitory effect on osteoblast formation and activity
TBI/cranio-spinal irradiation	Direct inhibitory effect on osteoblast formation and activity, decrease in growth hormone and IGF-1 production
Corticosteroids	Apoptosis of osteoblasts; inhibition of osteoblastogenesis; decrease in calcium levels due to inhibition of gastrointestinal absorption and increase in renal excretion

McClune et al. Bone Marrow Transplant 2011; 46: 1–9.

Bone Diseases

- Bone mineral loss increases risk of fractures just as it does in the general population
- Nontraumatic fractures observed in 10.6% of the population within 3 years after HCT
- Skeletal complications such as osteoporosis and osteoporotic fractures can adversely affect life quality

Cohen A et al. Osteoporosis Int. 2003;14:617-630.
Bhatia S. Hematology Am Soc Hematol Educ Program. 2014 ;2014(1):495-503.

Monitoring Recommendations

Organ system	Clinical measure	Screening guidelines - 2012 CIBMTR and NMDP recommendations
Skeletal	BMD	- Dual-photon densitometry (largely superseded by DEXA) at 1 year for all alloHSCT recipients - Subsequent testing determined by defects or to assess response to therapy
	Calcium / Vitamin D levels	- No recommendations - Physical activity, vitamin D and calcium supplementation recommended to prevent loss of bone density

NS Majhail et al. Bone Marrow Transplant. 2012;47(3):337-41.

Late Infections

- Important cause of late morbidity and mortality in both autologous and allogeneic HSCT recipients
- Adequate reconstitution of the cellular and humoral immune systems
  - 6–12 months after autologous HSCT
  - 2 years or more in allogeneic HSCT
- Further delayed in patients who develop GVHD

Majhail NS et al. Hematol Oncol Stem Cell Ther. 2017;10(4):220-227.

Late Infections

- Patients needing long-term immunosuppression for ongoing chronic GVHD are particularly at risk for infections by
  - Encapsulated bacteria
  - Fungi
  - Viruses
- Vaccinations should begin at 6–12 months after transplantation
  - Follow consensus recommendations for infection prevention in HSCT recipients
  - ASBMT (2009), IDSA (2013), ECIL (2017), CDC (2018)

Majhail NS et al. Hematol Oncol Stem Cell Ther. 2017;10(4):220-227.

Monitoring Recommendations

Organ system	Organism	Screening / preventive measures - 2012 CIBMTR and NMDP, 2009 ASBMT recommendations
Immune system	PCP	- Prophylaxis for initial 6 months after HSCT for all - Beyond 6 months for patients who have cGVHD or are receiving immunosuppressive therapy
	Viruses	- Prophylaxis of VZV reactivation for initial 1 year - CMV monitoring in patients at high risk for reactivation
	Encapsulated organisms	- Prophylaxis in patients with cGVHD or are receiving immunosuppressive therapy

- Immunization post transplant according to published guidelines

NS Majhail et al. Bone Marrow Transplant. 2012;47(3):337-41.

Limitations of Current Studies

- Data amongst Asian patients with regards to incidence of metabolic syndrome (MS), cardiovascular (CV) events and bone density loss post alloHSCT, as well as factors predisposing survivors to these complications are lacking

care
education
research

Singapore General Hospital
SingHealth

Characterization of Long-term Effects in Allogeneic Haematopoietic Stem Cell Transplantation (AlloHSCT) Survivors

Chong MF[1], Lim YJ[1], Linn YC[2], Ng HY[1]
[1]Department of Pharmacy, Singapore General Hospital, Singapore, [2]Department of Haematology, Singapore General Hospital, Singapore

INTRODUCTION

- Long-term survivors of allogeneic hematopoietic stem cell transplantation (alloHSCT) are at substantial risk for developing medical late effects such as metabolic syndrome (MS) and bone loss
- Potential contributing factors for these complications include pre-transplant conditioning, intensive immunosuppressive therapy and post-transplant endocrine dysfunction
- Recommendations for screening and preventive strategies for alloHSCT HSCT survivors have been made collectively by transplant experts from EBMT, CIBMTR and ASBMT
- Characterizing long-term effects in local alloHSCT survivors is important to guide interpretation and adaptation of international guidelines to local practice

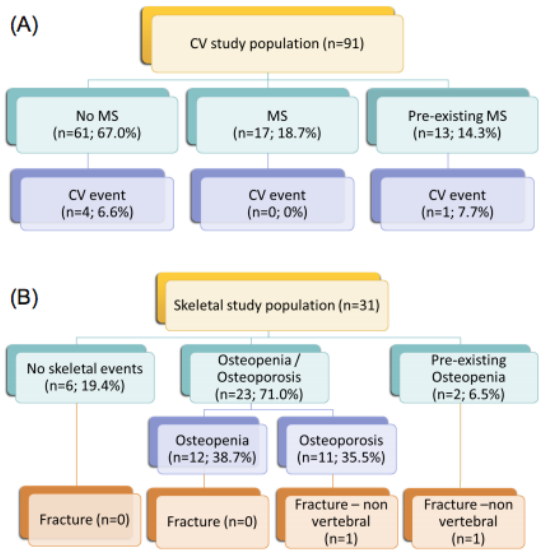
OBJECTIVES

- To determine the incidence of MS, CV events, bone density loss and fractures in patients who underwent alloHSCT for hematologic disorders
- To evaluate the potential association between patient factors and the development of MS, cardiovascular events, bone density loss and fractures

METHOD

- Retrospective review of patients ≥ 21 years who underwent alloHSCT between January 2011 and December 2016, with a minimum follow up period of 6 months
- Patients with MS related data made up the CV study population, whereas patients with bone loss related data made up the skeletal study population

RESULTS (cont'd)



Incidence of MS and CV events 15.4% and 5.5% respectively

- Median follow up 3.6 years (0.53 – 41.3)
- Median time to MS diagnosis = 356 (44 – 1792) days post alloHSCT

Incidence of bone loss and fractures 74.2% and 6.5% respectively

- Median follow up of 4.8 years (1.4 – 6.7)

Figure 1: Incidence of chronic health conditions after alloHSCT (A) Incidence MS and CV events (B) Incidence of bone loss and fractures

Baseline abdominal obesity, elevated triglycerides and fasting hyperglycemia were significantly associated with development of MS post alloHSCT

Objectives

- Primary objective:
  - Determine the incidence of MS, CV events, bone density loss and fractures in a cohort of patients who underwent alloHSCT for hematologic disorders
- Secondary objectives:
  - Evaluate the potential association between patient/transplant factors and development of MS, cardiovascular events, bone density loss and fractures

Methodology

- Retrospective review of patients ≥ 21 years who underwent alloHSCT between January 2011 and December 2016, with a minimum follow up period of 6 months
- **Patients with MS related data made up the CV study population, whereas patients with bone loss related data made up the skeletal study population**
- All analyses were performed using SPSS version 23

IDF/AHA 2009 Criteria for Metabolic Syndrome

	IDF/AHA 2009
Definition	**≥ 3 risk factors**
Risk factor	
Abdominal obesity	Male: ≥ 90 cm, Female: ≥ 80 cm (Asians) BMI ≥ 27.5kg/m^2 = high risk (WHO 2004) – surrogate
Triglycerides	≥ 150 mg/dL (≥ 1.7 mmol/L) or drug treatment for elevated levels
HDL cholesterol	Men: < 40 mg/dL (< 1.0 mmol/L) or drug treatment for reduced levels Women: < 50 mg/dL (< 1.3 mmol/L) or drug treatment for reduced levels
Blood pressure	≥ 130/ ≥ 85 mm Hg or drug treatment for HTN
Fasting glucose	≥ 100 mg/dL (≥ 5.6 mmol/L) or drug treatment for DM

Alberti KG et al. Circulation 2009; 120: 1640–1645.
Lee J et al. Clin endocrinol. 2008;69(2):225-230.
WHO Expert Consultation. Lancet. 2004;363(9403):157-63.

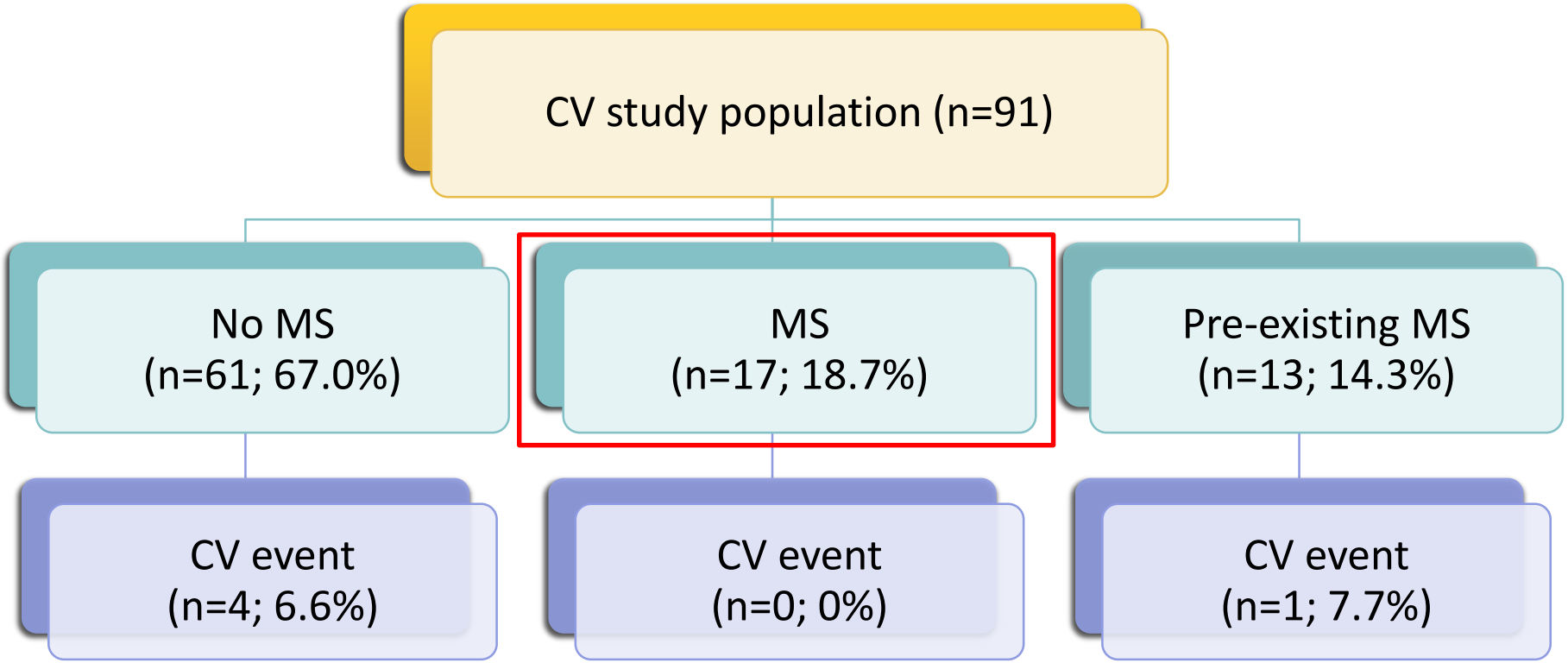
Results – Study population

Characteristic	All patients (n=95)		No MS (n=61)		MS (n=17)		Pre-existing MS (n=13)		*p*-value
	n	Percent or Range	n	Percent or Range	n	Percent or Range	n	Percent or Range	
Median age, yr	50	21-68	**48**	21-66	**51**	27-67	**59**	38-68	**0.005**
Race									
Chinese	73	76.8%	47	77.0%	13	76.5%	9	69.2%	0.300
Malay	7	7.4%	6	9.8%	0	0%	1	7.7%	
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%	0.543
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%	
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%	0.595
Bone marrow	5	5.3%	4	6.6%	1	5.9%	0	0%	
Cord blood	6	6.3%	6	9.8%	0	0%	0	0%	

Results – Study population (cont'd)

Characteristic	All patients (n=95)		No MS (n=61)		MS (n=17)		Pre-existing MS (n=13)		*p*-value
	n	Percent or Range	n	Percent or Range	n	Percent or Range	n	Percent or Range	
Conditioning regimen									
Myeloablative	29	30.5%	23	37.7%	3	17.6%	1	7.7%	
Non-myeloablative / Reduced intensity	66	69.5%	38	62.3%	14	82.4%	12	92.3%	0.378
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	0-2061	84	0-1555	106	0-1322	34	0-2061	0.839

Results – Primary Objective



- Median follow up 3.6 years (0.53 – 41.3)
- Total incidence of CV events = (5/91) x 100 = 5.5%; All CHD
- Median time to diagnosis of MS = 356 (44 – 1792) days post alloHSCT

Discussion – Primary Objective

MS

Our study:

Incidence – **18.7%**

Prevalence – 33%

Published data:

Incidence –
17 – 48%

Prevalence –
7.5 – 49%

CV Events

Our study:

Incidence – 5.5%

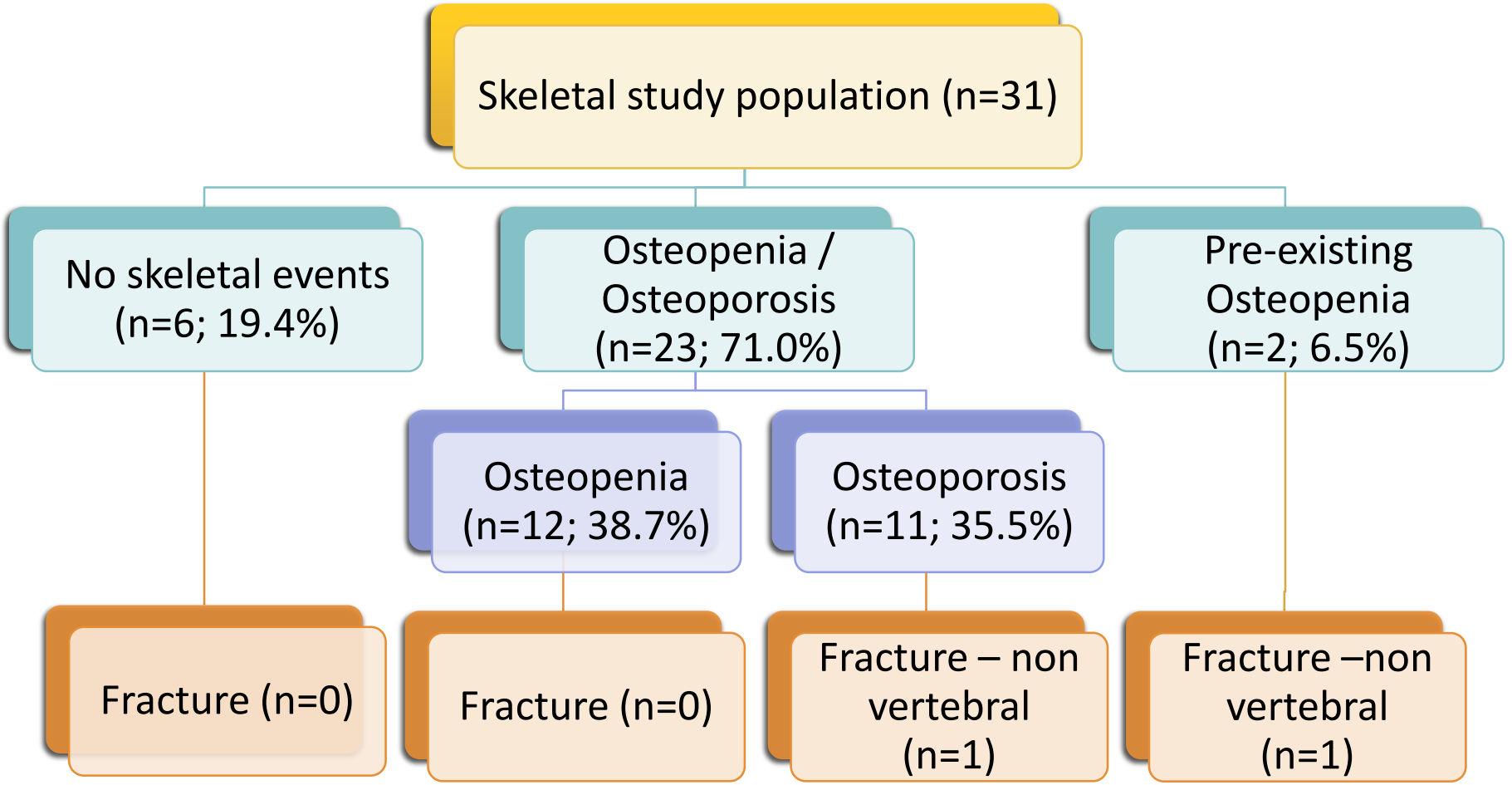
Published data:

Incidence –
3.6 – 7.5%

Tichelli A et al. Haematologica. 2008;93(8):1203-10.
Tichelli A et al, Blood. 2007 Nov 1;110(9):3463-71.
71.

DeFilipp Z et al. Bone Marrow Transplant. 2017;52(2):173-182.
McMillen KK et al. Metab Syndr Relat Disord. 2014;12(7):367-

Results – Primary Objective (cont'd)



Total incidence of fractures: (2/31) x 100 = 6.5%

Discussion – Primary Objective

Bone Loss

Our study:

Osteopenia – **38.7%**

Osteoporosis – **35.5%**

Published data:

Osteopenia – 42 – 50%

Osteoporosis – 25 – 32%

Fracture/ AVN

Our study:

Fractures – **6.5%**

AVN – 3.2%

Published data:

Fractures – 28.6%

AVN – 4 – 19%

McClune et al. Bone Marrow Transplant 2011; 46: 1–9.
NS Majhail et al. Bone Marrow Transplant. 2012;47(3):337-41.

Claudia M et al. Blood. 2004;103:3635-3643

Results – Secondary Objectives (cont'd)

Variables	Univariate Analysis		Multivariate Analysis (Adjusted for pre-existing MS)	
	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

- Underscores importance of controlling risk factors pre-transplant so as to optimize outcomes after alloHSCT.

Results – Secondary Objectives (cont'd)

n (%)	(A) Pre-transplant	(A) Post-transplant	(B) Pre-transplant	(B) Post-transplant	(C) Pre-transplant	(C) Post-transplant	Total pre-transplant	Total post-transplant
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 (78.7)
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)

Study	Year	N	Age	Stem cell source (n)	Median time after HSCT, yr	Treated with TBI	P / I	MS, %	Other
Taskinen M et al. (14)	2000	23	10-32	Allo	10.8	78	P	39	-
Taskinen M et al. (32)	2007	31	7-34	Allo	6	90	P	39	48% developed GH deficiency (75% with MS)
Oudin C et al. (33)	2011	60	18-41	Allo (39), auto (21)	15.4	72	P	15	-
Bajwa R et al. (34)	2012	160	5-28	Allo (99), auto (70)	7	37	P	7.5	17% developed GH deficiency
Frisk P et al. (35)	2012	18	17-37	Allo (3), auto (15)	18.2	100	P	17	39% treated with radiation
Paris C et al. (10)	2012	69	6-25	Allo (59), auto (10)	4	55	P	32	Low HDL most co component. Corti use before or afte was most significa factor for MS
Oudin C et al. (12)	2015	170	24.8 ± 5.4	Allo (124), auto (46)	14.5 (mean)	73	I	17	9% treated with cranial/craniospin GH deficiency ass increased MS risk
Higgins K et al. (31)	2005	16	25-54	Allo (13), auto (3)	6 (mean)	93	P	25	**Hypertriglyceridemia most common**
Annaloro C et al. (8)	2008	85	26-63	Allo (39), auto (46)	9	78	P	34	**Hypertriglyceridemia most common**
Majhail NS et al. (9)	2009	86	21-71	Allo	3	77	P	49	**Hypertriglyceridemia most common**
McMillen KK et al. (11)	2014	785	18-74	Allo	-	48	I	48% (at day 80) 40% (at 1 year)	**Hypertriglyceridemia most common**

Important to monitor lipid panels routinely in this patient population

Results – Secondary Objectives (cont'd)

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 – 1000)	0.02
Baseline BMI	NA	0.038	1.9 (1.0 – 3.6)	0.06

- Baseline BMI 21.3 (16.2 – 26.7) vs 24.3 (21.3 – 34.2) in groups with and without post alloHSCT bone loss respectively
- Only female gender remained significant on multivariate analysis, after adjusting for pre-existing osteopenia
- Other factors were not significantly different between the 2 groups

Limitations

- Retrospective study
  - Only associations, but not causal relationships can be determined
  - Accuracy and completeness of data collection is largely dependent on high quality existing data
- Small sample size of this study
- Information bias
  - Patients without MS or BMD data were excluded

Limitations

- BMI may not be a sufficient measure of abdominal obesity and muscle loss
  - Waist circumference preferred – emphasizes visceral adipose deposits
  - Does not measure sarcopenia – change in strength and mass of skeletal muscles
  - Studies reporting waist circumference at time of and following HSCT are limited – BMI a possible surrogate

Armenian SH et al. Biol Blood Marrow Transplant. 2017;23(2):201-210.

Learning Points from Study

- Suboptimal control of CV risk factors at baseline potentially increases the risk of developing MS post alloHSCT
- Females are at increased risk of developing bone loss post alloHSCT
- Importance of developing institution guideline and methods for implementation to improve long term outcomes
  - Screening chart
  - Long-term follow up clinic

Clinical Recommendations: Cardiovascular Complications

- **Pre-transplant**
  - Clinical Hx, FH, symptoms
  - Control pre-existing HTN, DM, dyslipidaemia, obesity
- **Post transplant - Screening and treatment**
  - BP
  - Lipid profile
  - HbA1c, glucose
  - Waist circumference / BMI
  - Endocrine Evaluation:
    - Gonadal and thyroid function, growth hormone
- **Risk modification**
  - Diet – low fat, low cholesterol
  - Exercise
  - Avoid smoking
  - Limit alcohol

DeFilipp Z et al. Bone Marrow Transplant. 2017;52(2):173-182.
NS Majhail et al. Bone Marrow Transplant. 2012;47(3):337-41.

Clinical Recommendations: Skeletal Complications

- **Pre-transplant**
  - Identify patients at risk – female, low baseline BMI
- **Post transplant - Screening and treatment**
  - BMD
  - Endocrine evaluation
  - Consider earlier monitoring in patients with cGVHD
- **Risk modification**
  - Calcium and vitamin D supplementation
  - Exercise
  - Avoid smoking, Limit alcohol

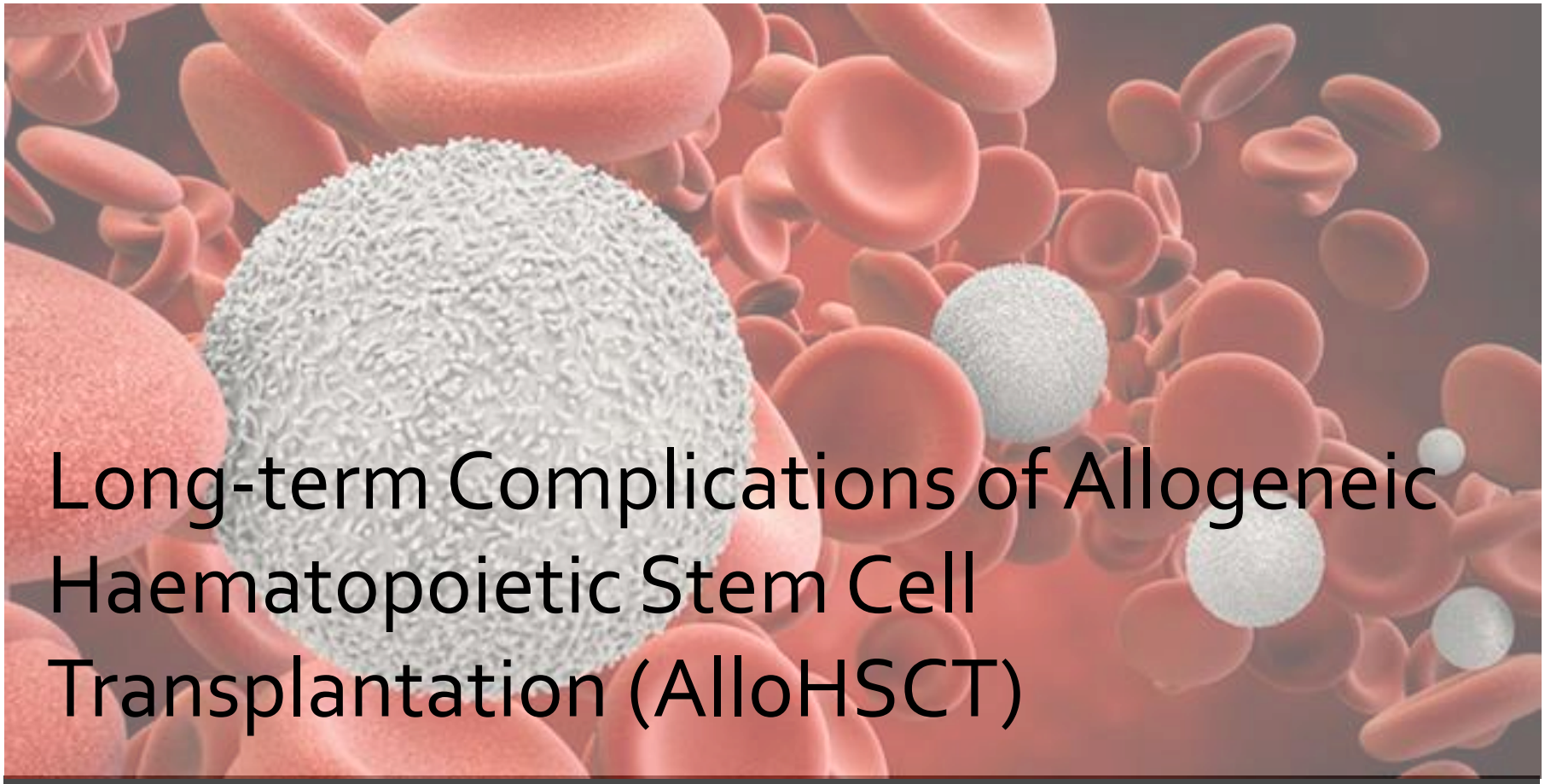
NS Majhail et al. Bone Marrow Transplant. 2012;47(3):337-41.

Take Home Message

- Advances in alloHSCT and supportive care strategies have resulted in improvements in HSCT outcomes and an expanding population of long term survivors
- However, HSCT survivors remain at risk for late complications and premature mortality
- HSCT survivors need individualized and patient-centric follow-up care provided through a multidisciplinary collaborative care model that considers their preferences and needs

Take Home Message

- A treatment summary and survivorship care plan can facilitate care coordination
- Provides comprehensive summary of
  - Patient's diagnosis
  - Pre-transplant therapies, transplant course, and post transplant complications
  - Evaluations recommended for late effects monitoring
  - Provider responsible for conducting evaluation



Long-term Complications of Allogeneic Haematopoietic Stem Cell Transplantation (AlloHSCT)

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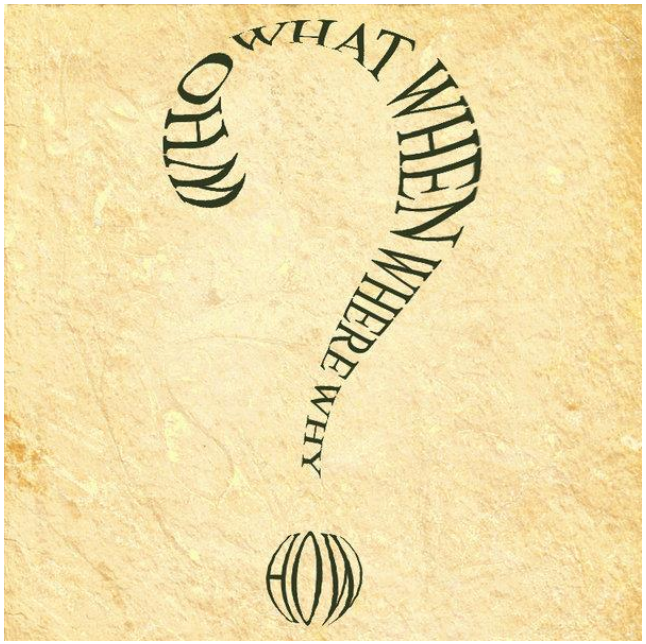
Questions



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