



NASEM Stem Cell Treatment & Disability: Patterns of Recovery in Patients Treated with Hematopoietic Stem Cells

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Fred Hutchinson Cancer Research Center
November 15, 2021

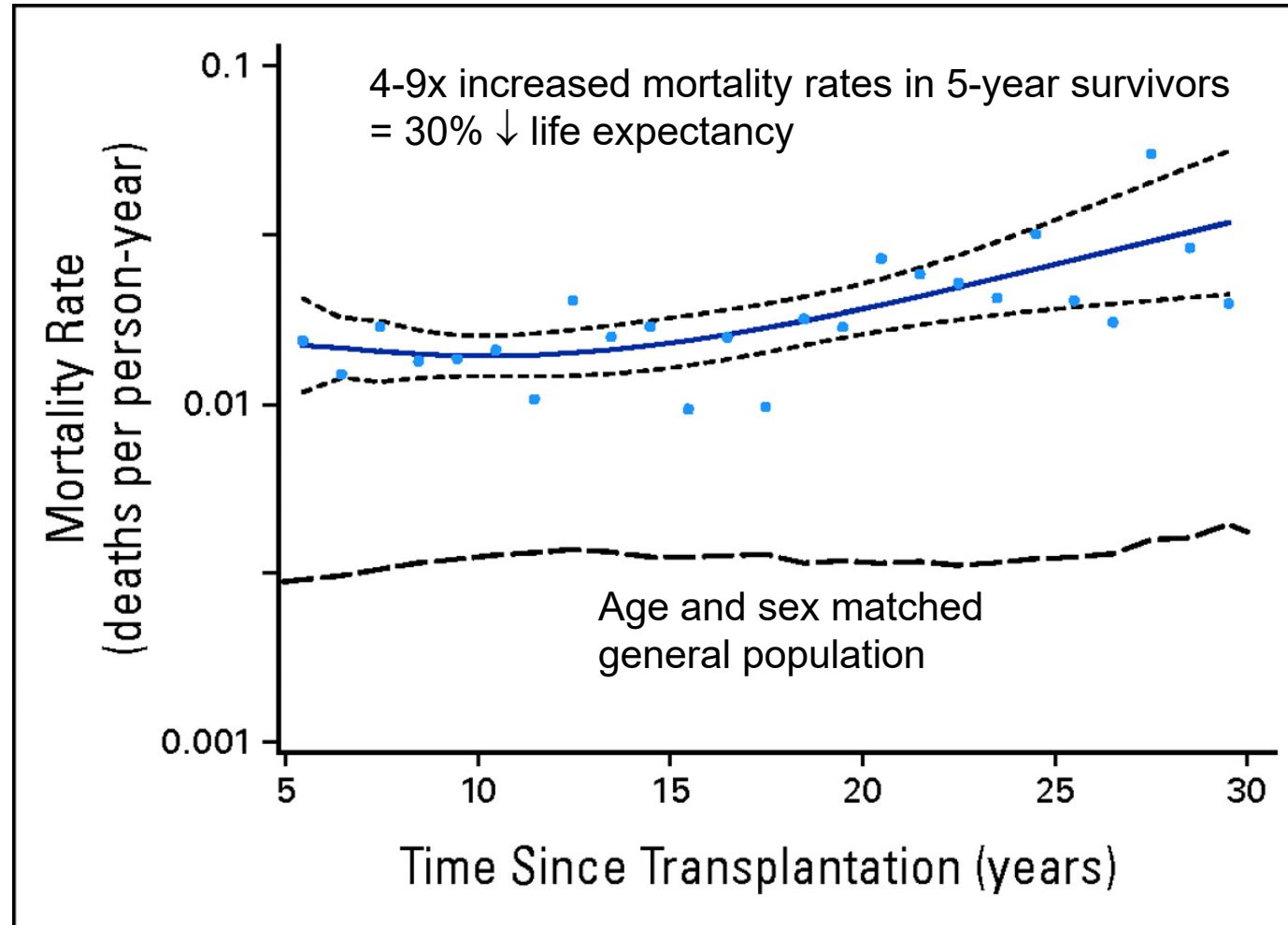
Disclosures

Year	Source	Topic	Activity
2018	Pfizer	inotuzumab AML	Consulting
2018	Kadmon	belumosudil (KD025)	Consulting
2018	Millennium Pharmaceuticals Inc.	ixazomib	Research funding
2018	Novartis Inc.	ofatumumab	Research funding
2018	Amgen Inc.	efavaleukin alfa (AMG592)	Travel and lodging
2018 -	Kadmon Corporation LLC	belumosudil (KD025)	Research funding
2018 -	Amgen Inc.	efavaleukin alfa (AMG592)	Research funding
2019 -	Pfizer Inc.	glasdegib	Research funding
2019 -	Syndax Pharmaceuticals Inc.	axatilimab (SNDX5692)	Research funding
2019 -	Incyte	ruxolitinib	Research funding
2019 -	AstraZeneca Pharmaceuticals LP	acalabrutinib	Research funding
2021	Mallinckrodt	extracorporeal photopheresis	Consulting
2021	Amgen	efavaleukin alfa (AMG592)	Consulting
2021-	National Marrow Donor Program	member	Board of Directors

Successful hematopoietic cell transplantation

- Alive, disease-free
- Restore life expectancy
- Normal physical and mental functioning
- Good quality of life
- Return to social roles – parent, worker, student

Increased mortality rates persist



Martin et al. JCO 2010; 28: 2011

Among 2-year DFS,
subsequent survival:

Autologous

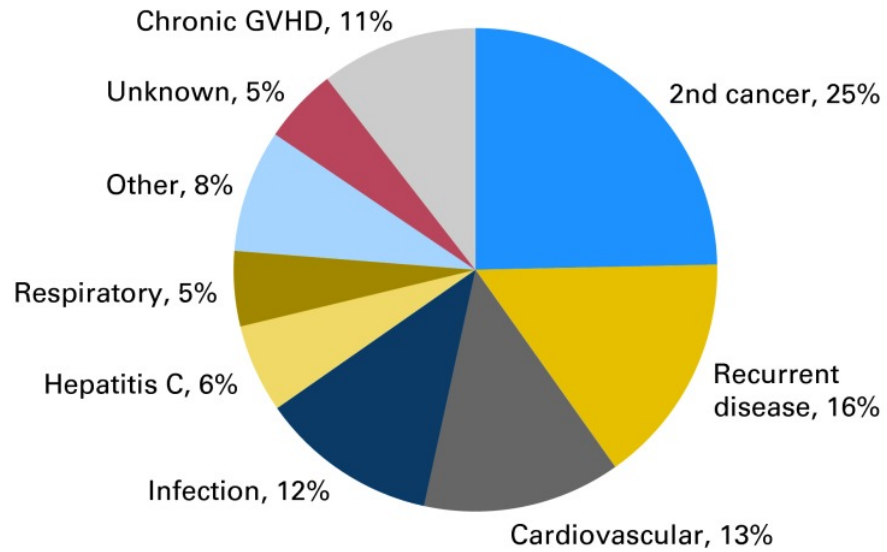
70-80% at 10 years

Allogeneic

85% at 10 years

80% at 15 years

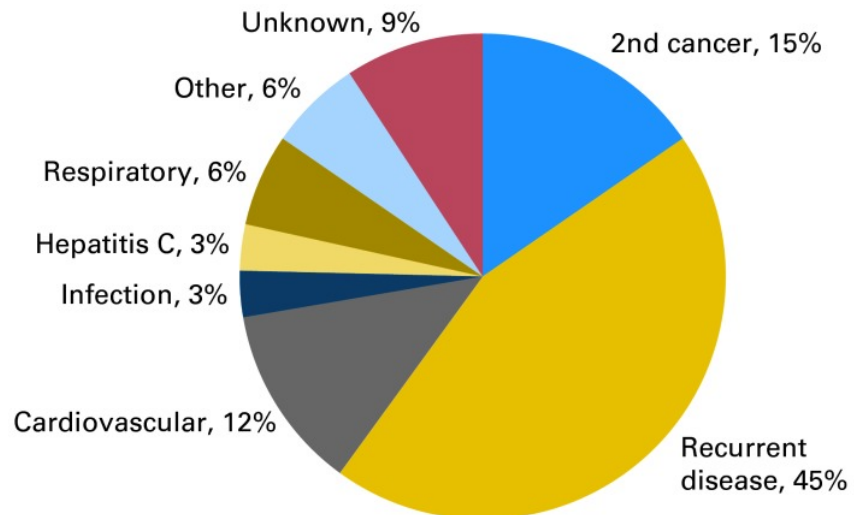
Martin et al, JCO 2010; 28: 1011-1016
Atsuta et al, BBMT 2016; 22: 1702-1709
Myers et al, Cancer 2017; 124: 816-825
Holmqvist et al, Blood 2018; 131: 2720-2729
Holmqvist et al, JAMA Onc 2018; 4: e182453
El-Asmar et al, BBMT 2019; 25: 2522-2526
Bhatia et al, JAMA Onc 2021; online

A**Allogeneic**

Late deaths (5 year DFS)

N=1,625 allogeneic recipients
(13% died, n=219)

N=342 autologous recipients
(19% died, n=65)

B**Autologous**

Martin et al. JCO 2010; 28: 2011
Syrjala et al. JCO 2012; 30: 3746

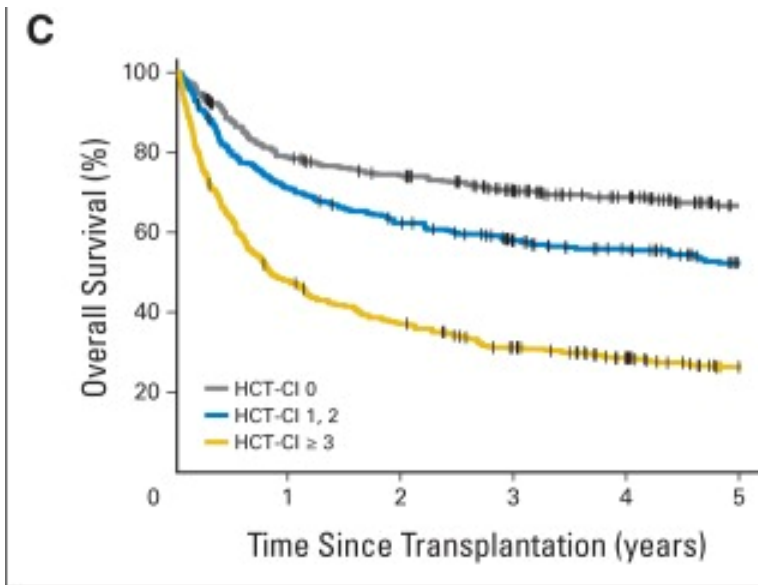
Successful hematopoietic cell transplantation

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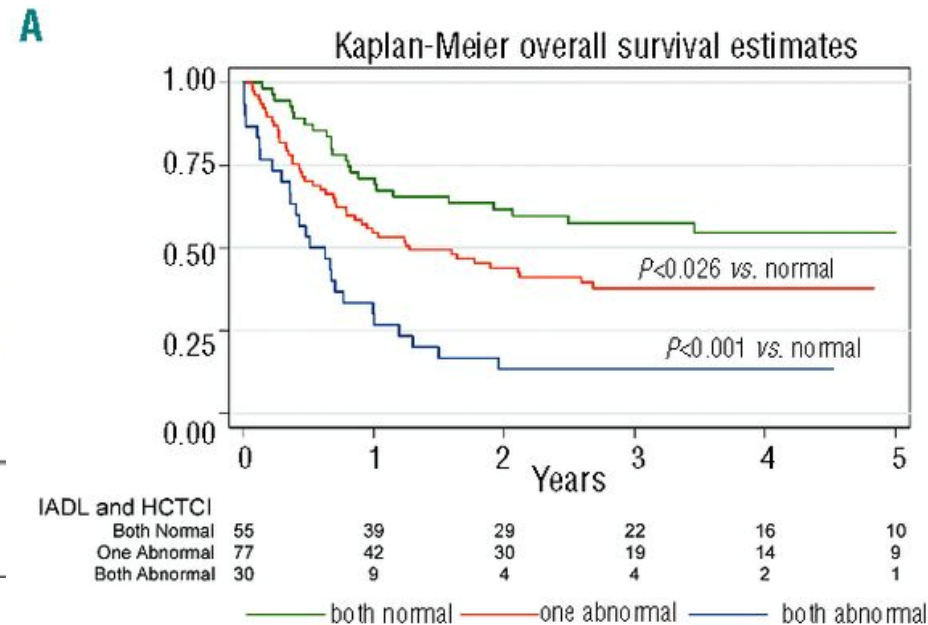
Many people are already disabled before HCT

- Most transplants are performed for hematologic malignancies
 - Cyclic pre-HCT chemo- and radiotherapy
 - Unable or not advised to work or go to school
- High rates of comorbidities, frailty, poor physical and mental quality of life
 - Correlate with complications, transplant-related mortality, survival
- Unlike some other life-saving medical procedures, HCT does not usually improve health while curing disease

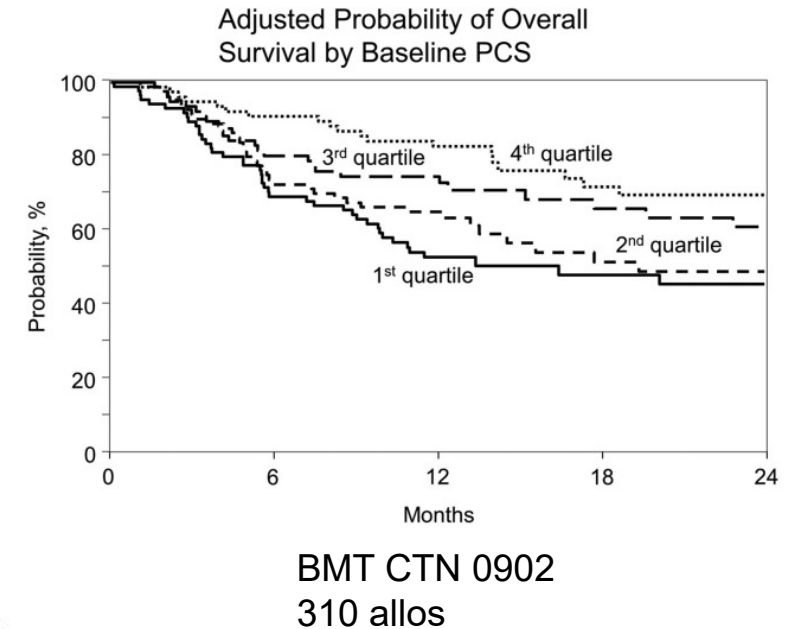
Pre-HCT CMB, frailty, QOL predict survival



Multi-institution
3,033 allo

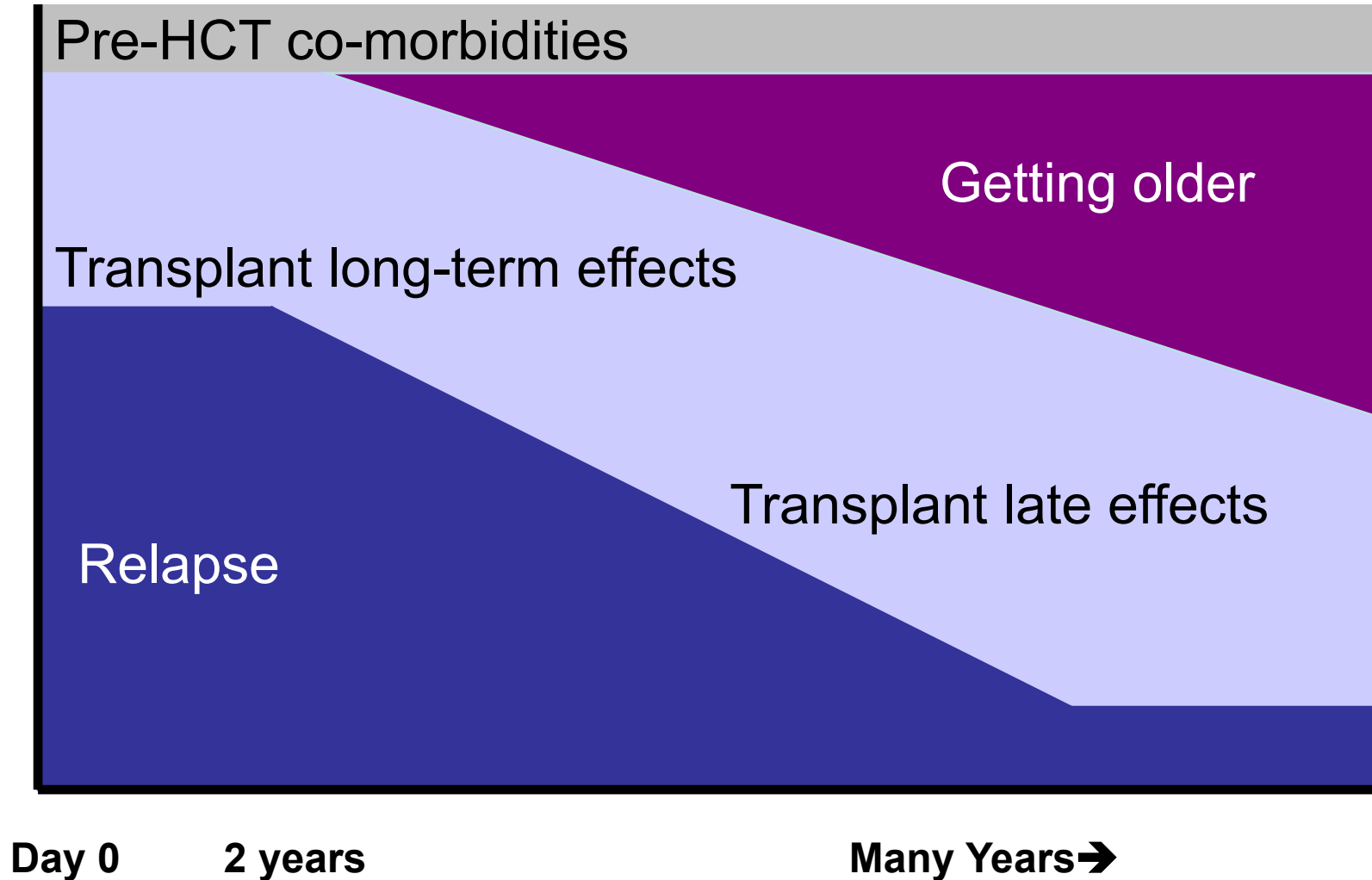


Single center
203 allo, >50 y/o



Sorrer M et al, JCO 2014; 32: 3249
Muffy L et al, Haematologica 2014; 99: 1373
Wood W et al. Cancer 2016; 122:91

Attributable disability



First 1-2 years after HCT

- How the transplant goes
 - The toll it takes – temporary or permanent co-morbidities
 - How the patient recovers
- Whether relapse occurs
- Whether chronic GVHD develops

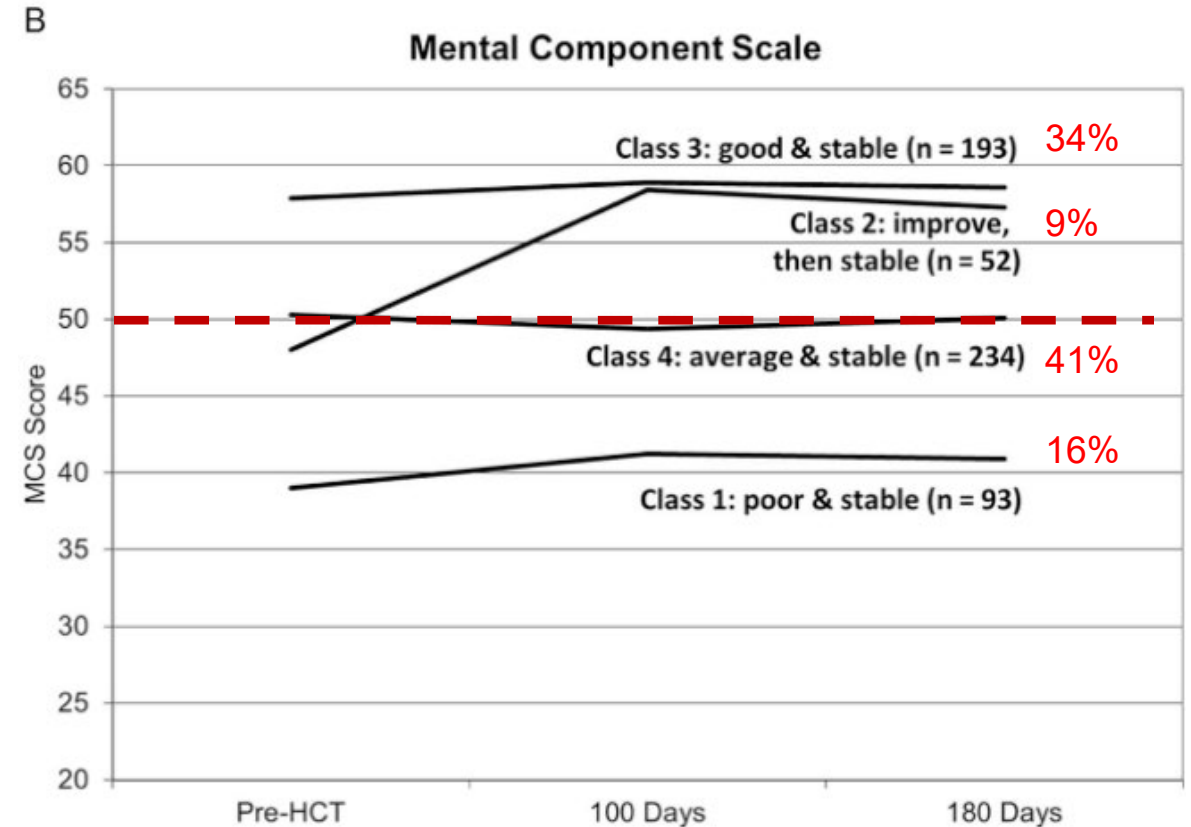
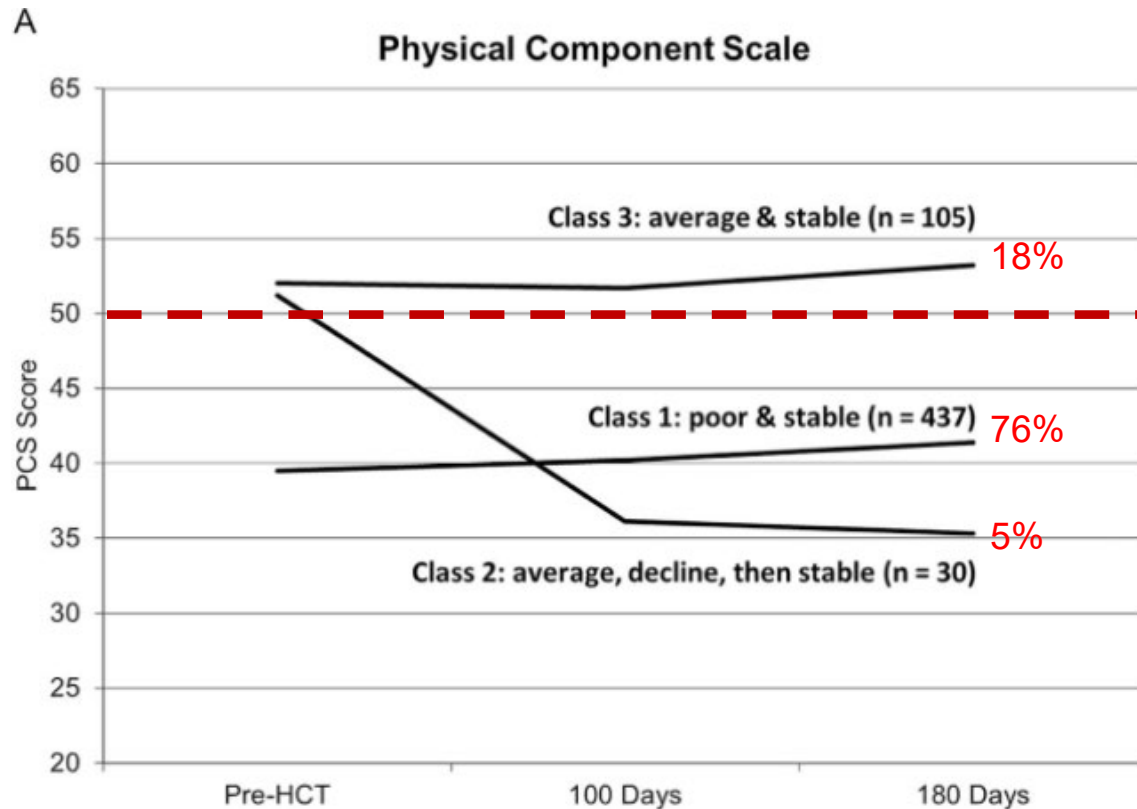


Clinical Research: Supportive Care

Trajectories of Quality of Life after Hematopoietic Cell Transplantation: Secondary Analysis of Blood and Marrow Transplant Clinical Trials Network 0902 Data



Heather S.L. Jim ^{1,*}, Steven K. Sutton ², Brent J. Small ^{2,3}, Paul B. Jacobsen ¹, William A. Wood ⁴, Jennifer M. Knight ⁵, Navneet S. Majhail ⁶, Karen L. Syrjala ⁷, Stephanie J. Lee ⁷



Changes in physical/mental functioning predict survival

OS*

Scale	HR for 10pt change (95% CI)	p-value
PCS	1.83 (1.40-2.40)	<0.001
MCS	1.43 (1.13-1.80)	0.003

TRM*

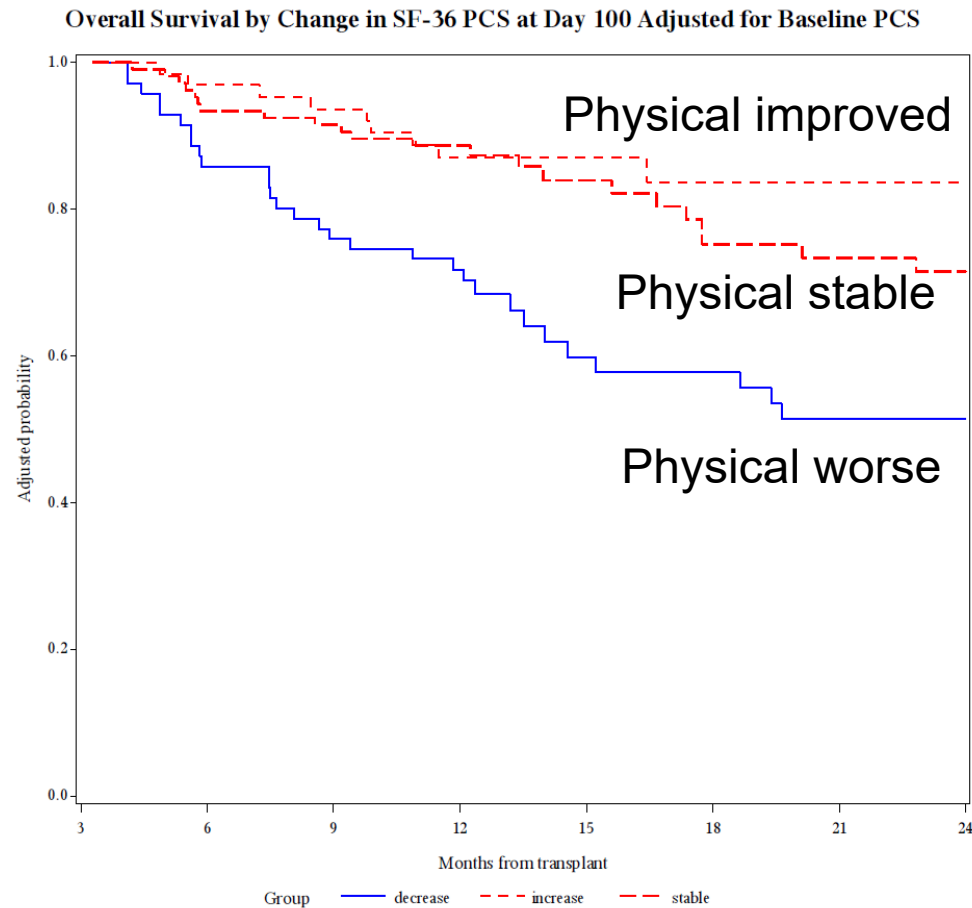
Scale	HR for 10pt change (95% CI)	p-value
PCS	3.57 (2.13-5.88)	<0.001

*models adjusted for baseline score, age, EBMT score, HCT-CI, DRI

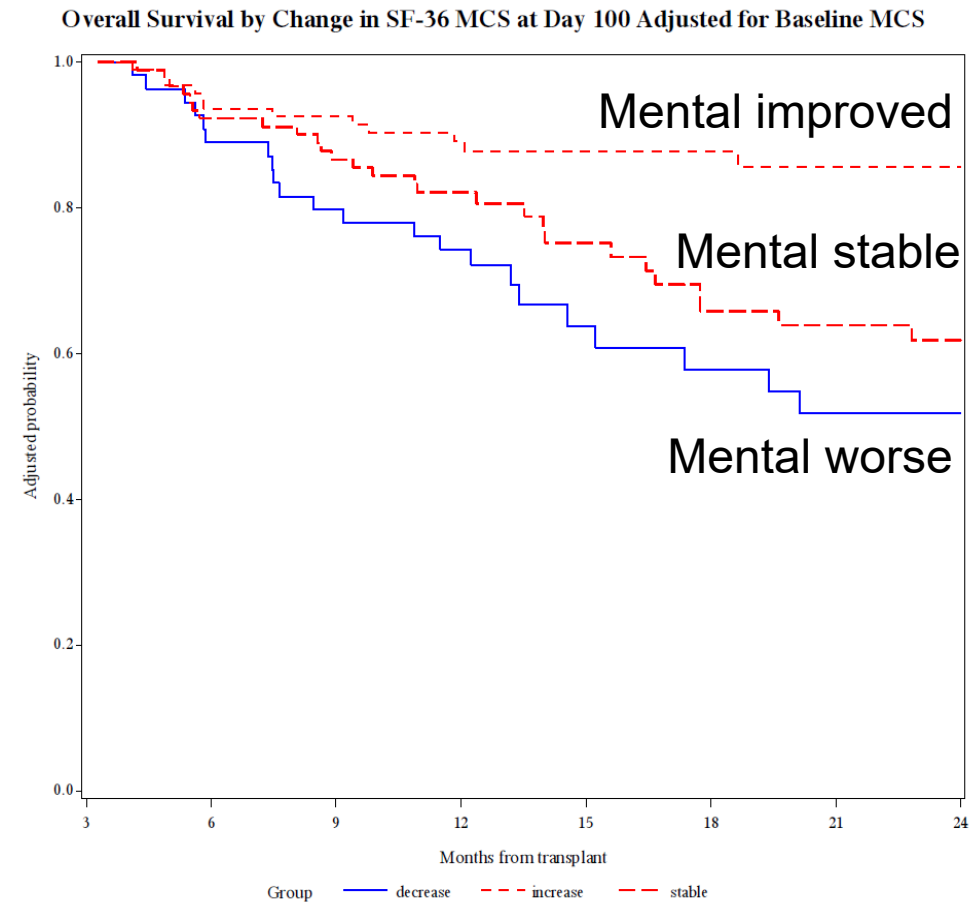
Changes in physical/mental functioning predict survival

27% died, median 8 mos

Decline in PCS = higher mortality



Stable or decline in MCS = higher mortality



Medication burden at 1 year (118 allos)

Median 6 (IQR 4-9) systemic meds

n (%)		n (%)	
Anti-infective	111 (94%)	Hormone	32 (27%)
Calcineurin inh	66 (56%)	Anti-Depress	31 (26%)
Prednisone	59 (50%)	Diabetes	18 (15%)
Anti-HTN	38 (32%)	Thyroid	15 (13%)
Bisphos	35 (30%)	Anti-Lipid	11 (9%)

84 (71%) on immunosuppression

88% of 1-year DFS
40% reduced intensity
53% unrelated donors

Recovery and Long-term Function After Hematopoietic Cell Transplantation for Leukemia or Lymphoma

JAMA 2004; 291: 2335

Karen L. Syrjala, PhD

Shelby L. Langer, PhD

Janet R. Abrams, PsyD

Barry Storer, PhD

Jean E. Sanders, MD

Mary E. D. Flowers, MD

Paul J. Martin, MD

- 319 pre-HCT
- 94 at 5 yrs
- 20% autos/80% allos

Figure 4. Respondents With Physical Limitations Over Time, According to Presence or Absence of Depressive Symptoms at Baseline

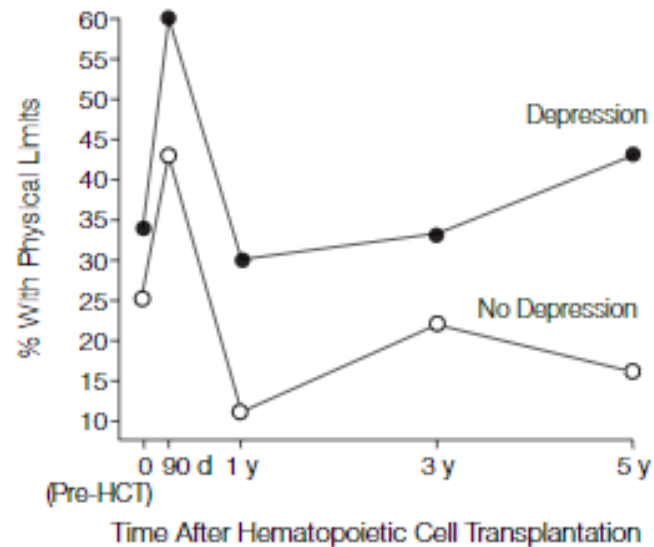
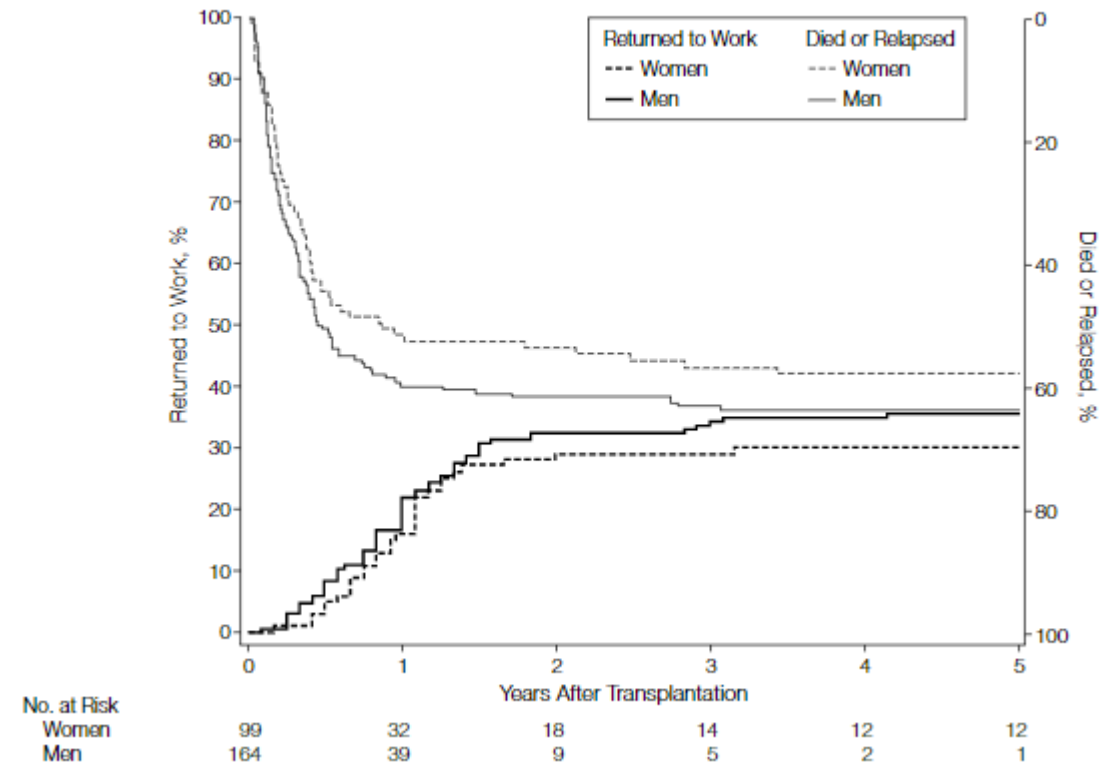


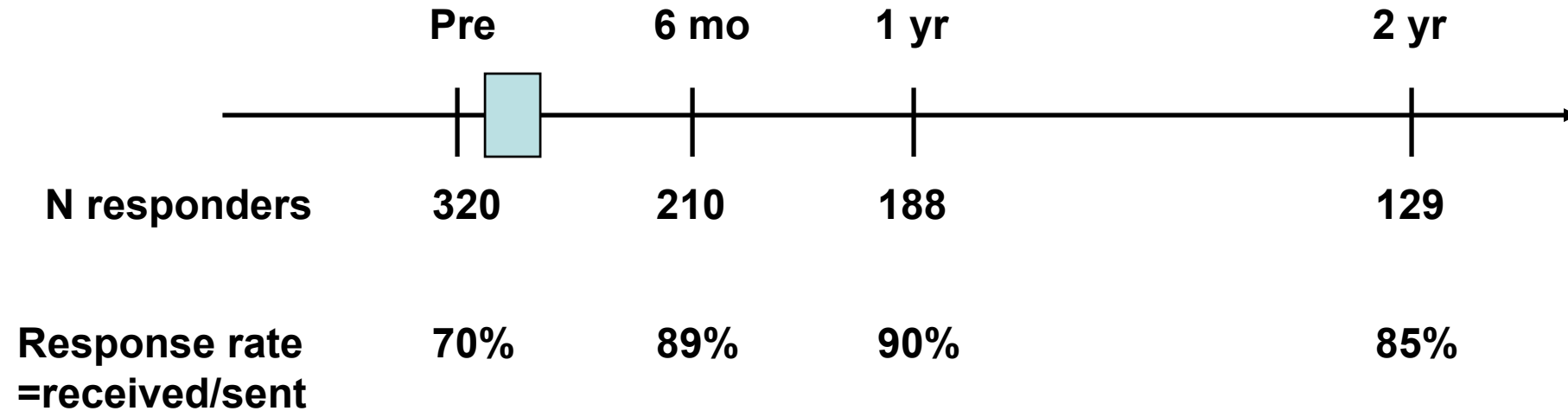
Figure 6. Cumulative Incidence of Return to Full-time Work as a Function of Sex



Recovery After Stem-Cell Transplantation for Hematologic Diseases

By Stephanie J. Lee, Diane Fairclough, Susan K. Parsons, Robert J. Soiffer, David C. Fisher, Robert L. Schlossman, Joseph H. Antin, and Jane C. Weeks

JCO 2001; 19: 242-252



1996-1999

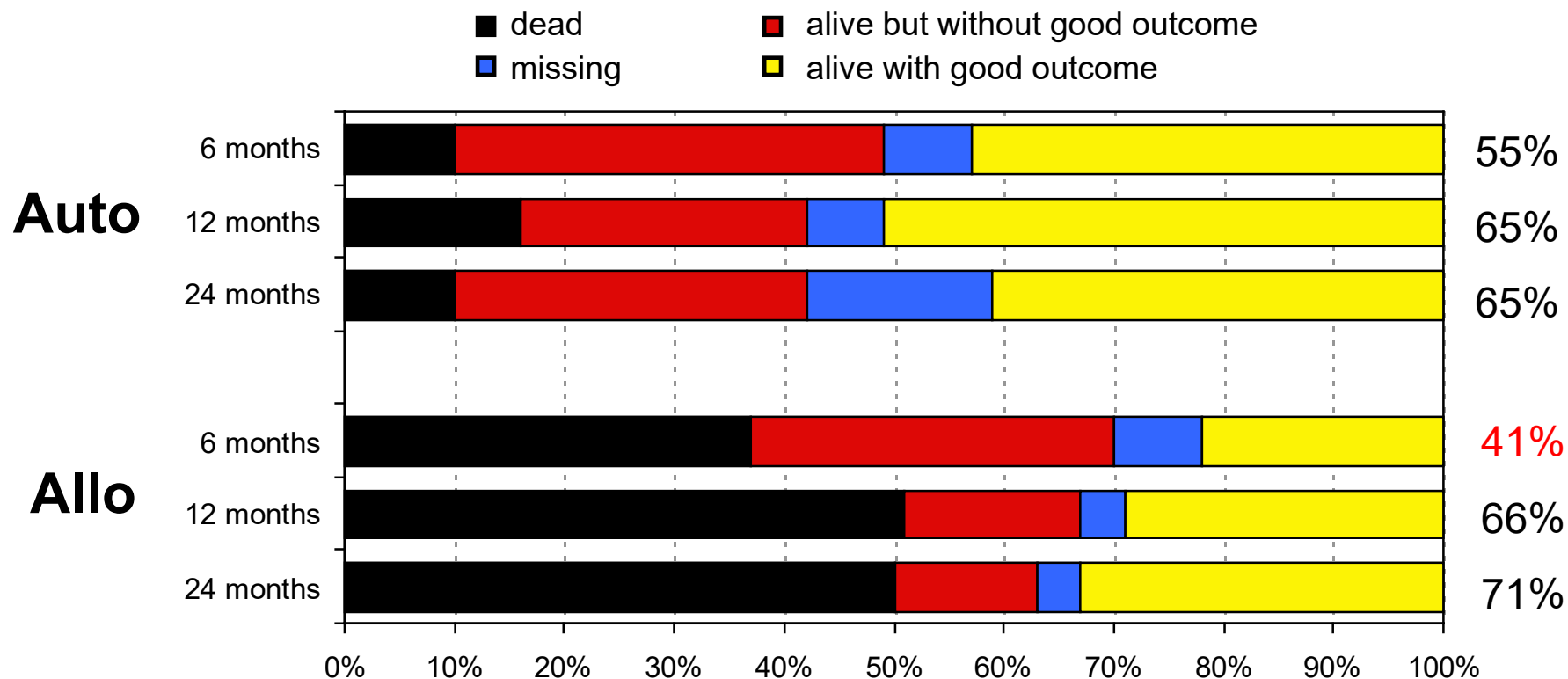
Autos (median age 51) and allos (median age 45)

94-96% White, 45-52% college educated

Not returning a survey was associated with relapse/death

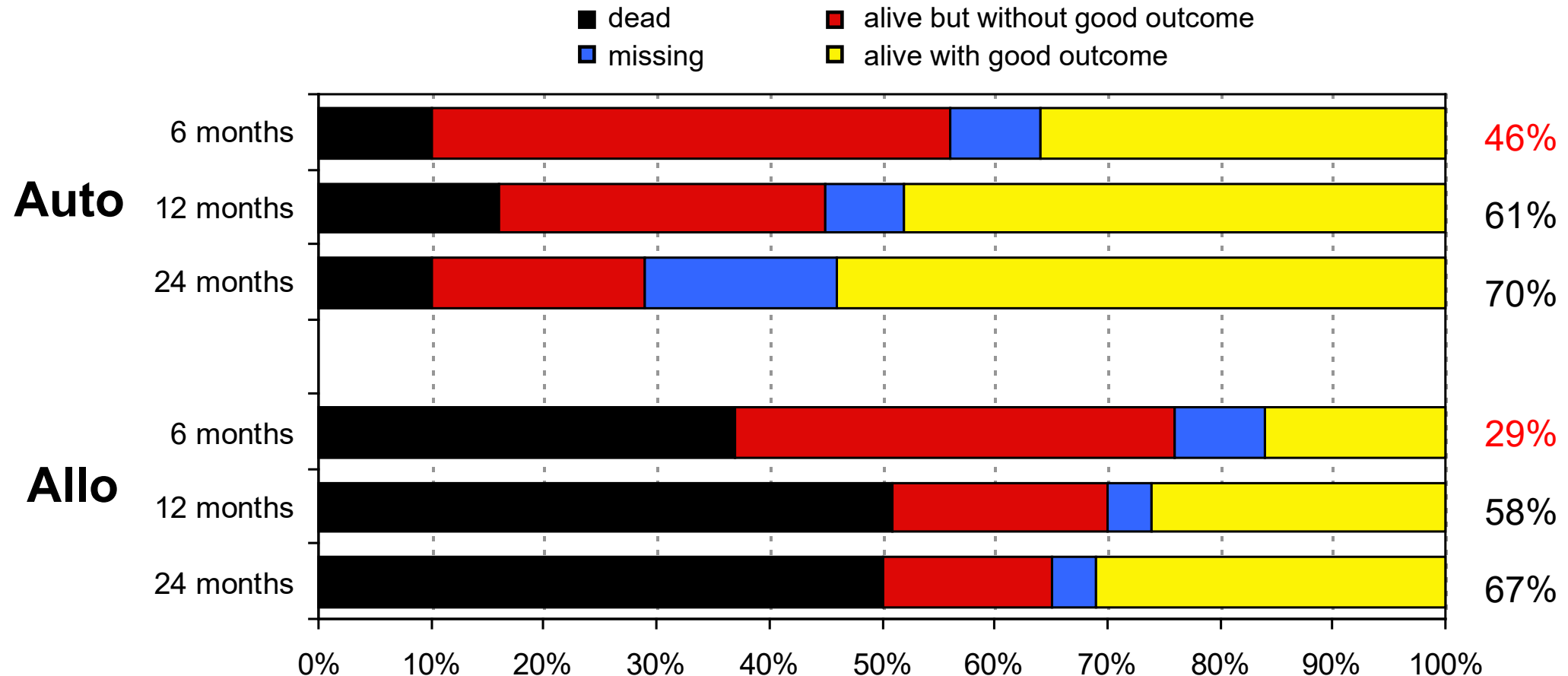
Some of the 2-year participants were converted to another study

“ I have recovered from my transplant”



“Somewhat or strongly agree” vs. “neutral, somewhat disagree, strongly disagree”

Back to school/ work/ homemaking



Our myeloablative allogeneic patients tell us:

- **At 6 months...**
 - **43% have very good or excellent health**
 - **44% are bothered a lot or extremely bothered by fatigue**
 - **41% have recovered from their transplant**
- **At 12 months...**
 - **58% have very good or excellent health**
 - **35% are bothered a lot or extremely bothered by fatigue**
 - **66% have recovered from their transplant**
 - **58% are back at school, work, homemaking**
 - **67% by 24 mos**

Our autologous patients tell us:

- **At 6 months...**
 - 37% have very good or excellent health
 - 42% are bothered a lot or extremely bothered by fatigue
 - 55% have recovered from their transplant
- **At 12 months...**
 - 46% have very good or excellent health
 - 30% are bothered a lot or extremely bothered by fatigue
 - 65% have recovered from their transplant
 - 61% are back at school, work, homemaking
 - 70% by 24 mos

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

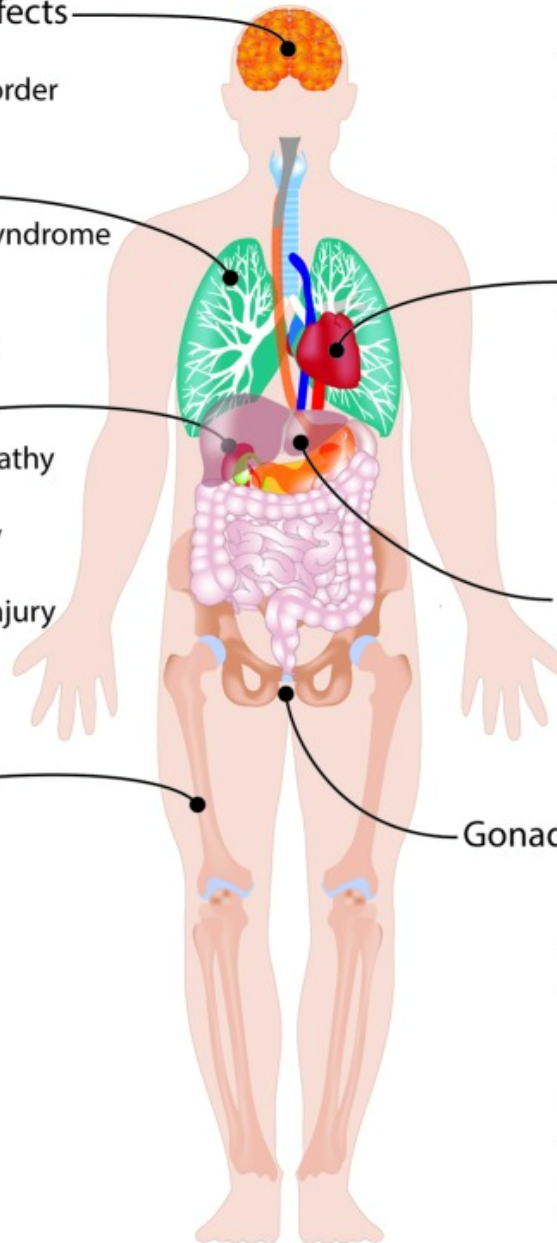
Liver diseases

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

Gonadal dysfunction/infertility

Infectious diseases

- *Pneumocystis jirovecii*
- Encapsulated bacteria
- Fungi
- Varicella-zoster virus
- Cytomegalovirus
- Respiratory syncytial virus
- Influenza virus
- Parainfluenza virus



Syrjala JCO 2005; 23: 6596

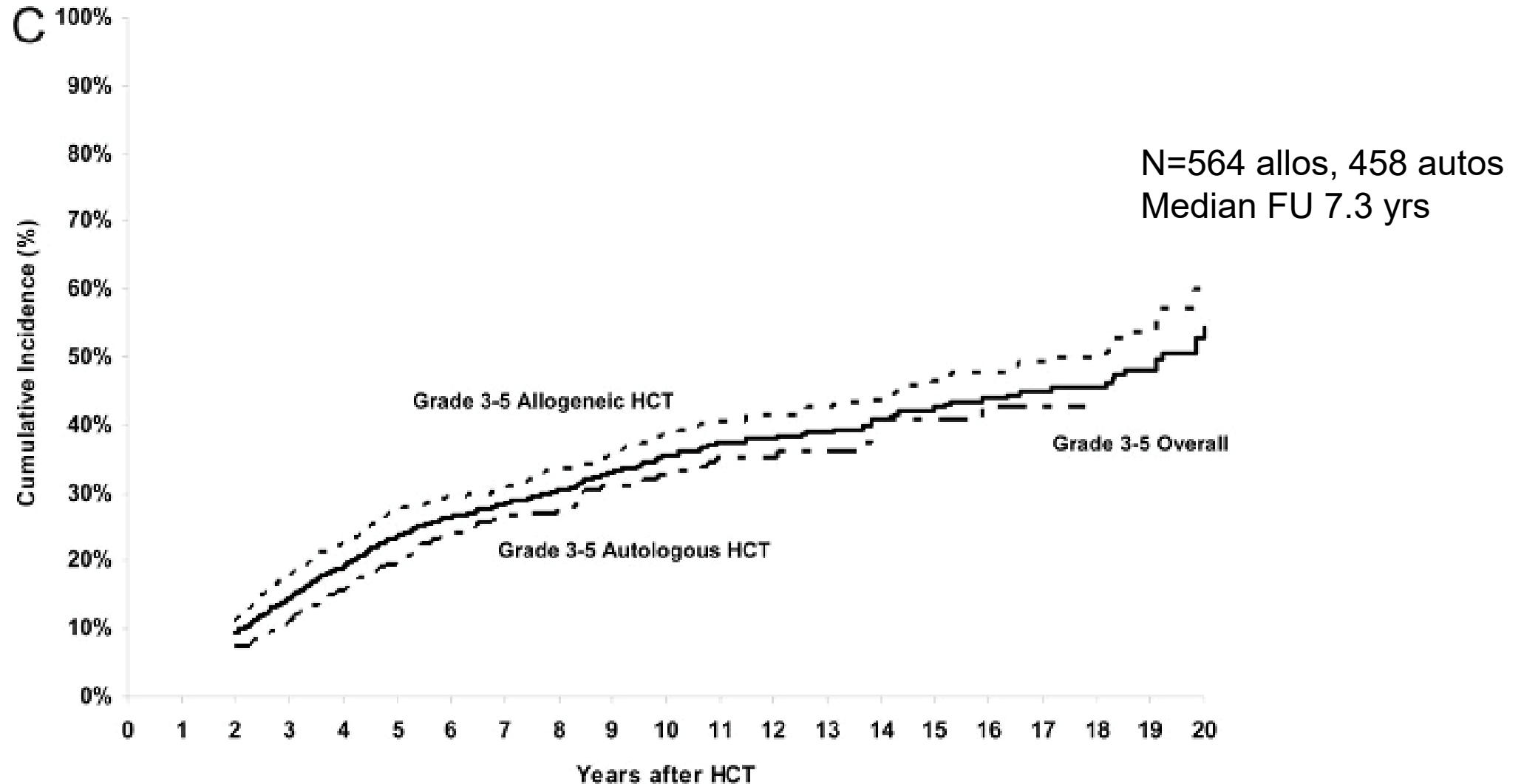
Baker Leukemia 2010; 24: 2039

Khera JCO 2011; 30: 71

Inamoto Haematologica 2017; 102: 614

Eissa Blood Adv 2017; 1: 2243

Chronic health conditions

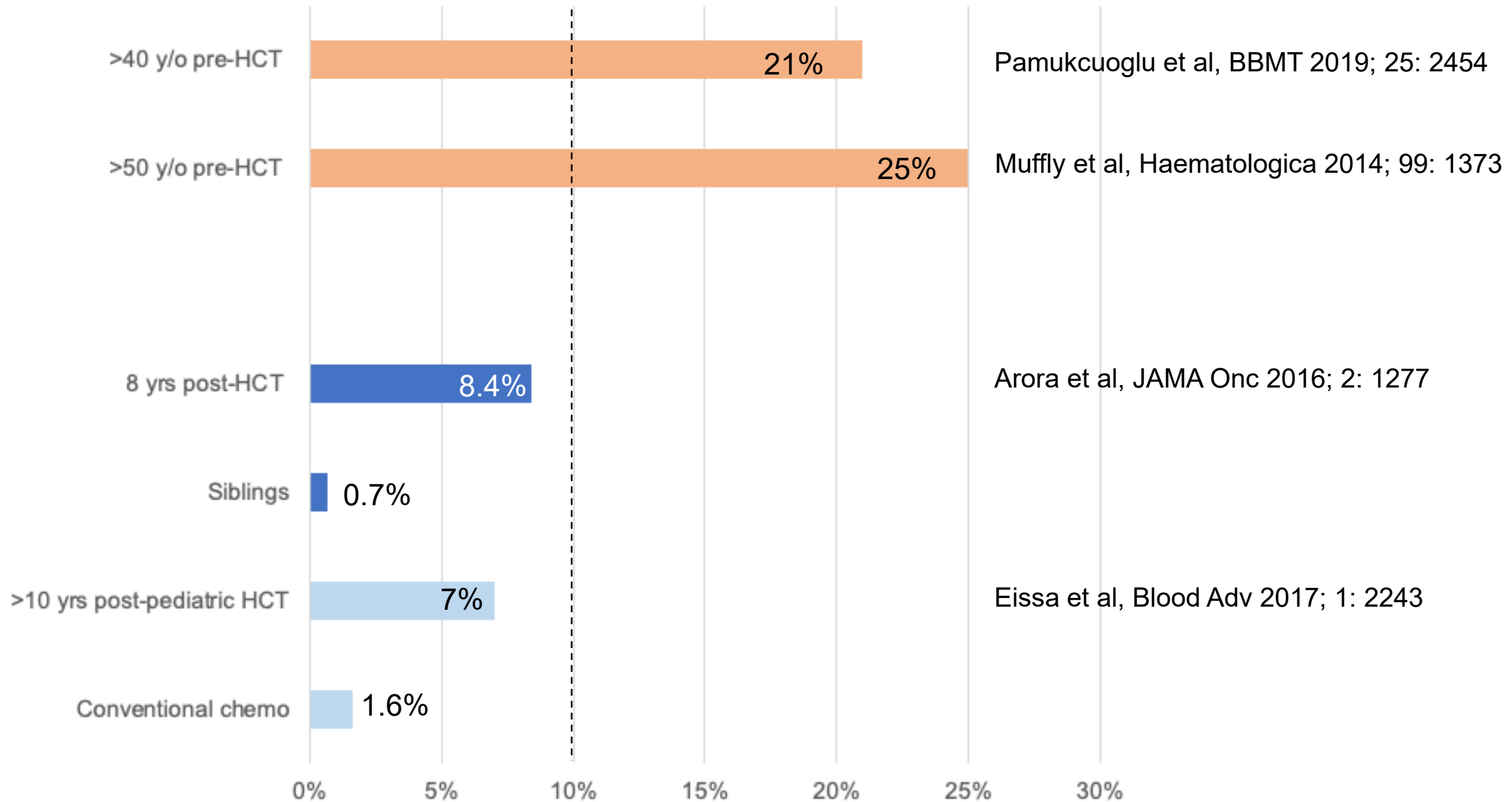


Grade 3-4: 3x rate in siblings

Sun CL et al, Blood 2010; 116: 3129

Frailty

- Premature aging: decreased physiologic reserve, more susceptible to stressors
- Characterized by exhaustion, weakness, slow walking speed, low physical activity, unintentional weight loss
- Associated with more chronic health conditions, higher mortality



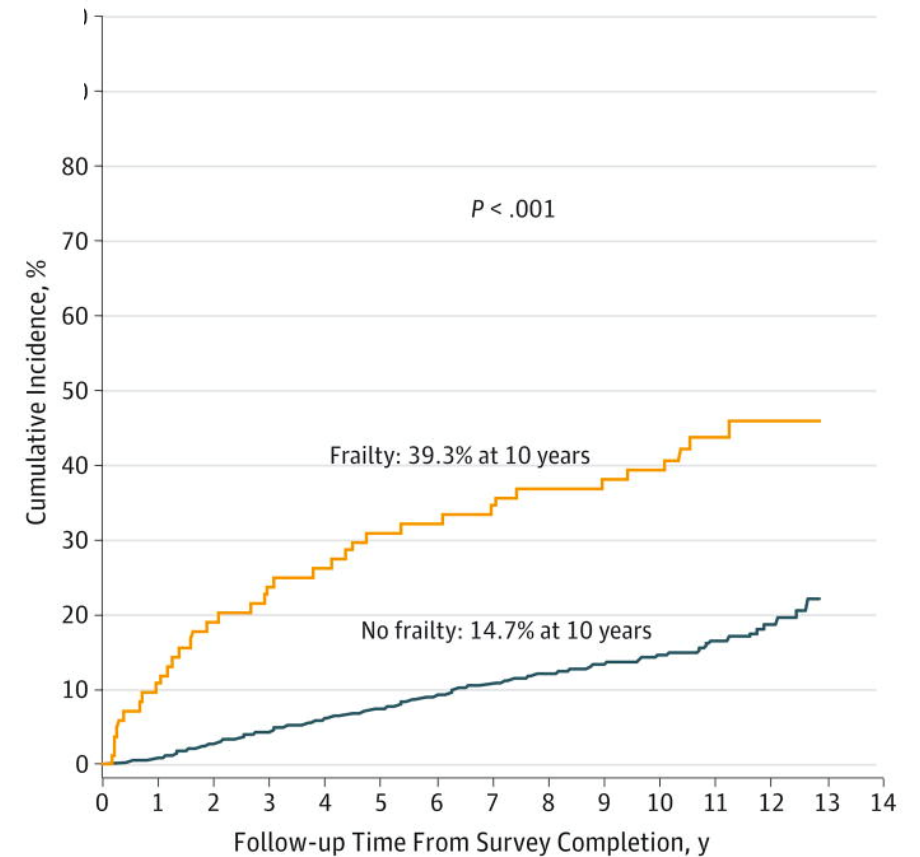
Physiologic Frailty in Nonelderly Hematopoietic Cell Transplantation Patients

Results From the Bone Marrow Transplant Survivor Study

Mukta Arora, MD, MS; Can-Lan Sun, PhD; Kirsten K. Ness, PhD; Jennifer Barano Teh, MD; Jessica Wu, BA; Lifen Francisco, BS; Siro H. Armanian, DO, MPH; Amy Schad, MA; Golnaz Namdar, MPH; Alysia Bosworth, BA; Linus Kuo, BA; Daniel J. Weisdorf, MD; Stephen J. Forman, MD; Smriti Bhatia, MD, MPH

JAMA Onc 2016; 2: 1277

- 8.4% frail by self-report
- Exhaustion, slowness, weakness
- Predictors:
 - Myeloma
 - Allo with chronic GVHD
 - Chronic health conditions
 - Low SES
- 39% vs. 15% mortality at 10 years



No. at risk														
Frail	84	84	75	68	64	62	58	57	55	53	51	45	29	16
Not frail	914	914	908	889	873	857	847	830	815	777	717	549	254	103

Successful hematopoietic cell transplantation

- Alive, disease-free
- Restore life expectancy
- Normal physical and mental functioning
- Good quality of life
- Return to social roles – parent, worker, student

Only 50-80% return to FT/PT work

First author	Design	Population	Conclusions; risk factors	Reference
Kirchhoff	Longitudinal	N=88 (auto/allo)	92% @ 5 years if FT pre-HCT; female, physical dysfunction	J Cancer Surv 2010; 4:43
Wong	Longitudinal	N=312 (auto/allo)	74% @ 3 yrs; older autos with lower pre-HCT income, allos with cGVHD	Blood 2010; 115: 2508
Morrison	Longitudinal	N=690, 79% auto	62% @ 1 year; hospitalizations, relapse, pain, fatigue	BBMT 2016; 22:1690
Lee	Longitudinal	N=152, allo	47% @ 5 yrs; peripheral blood	JAMA Onc 2016; 2: 1583
Tichelli	X-sec survey	N=203, >5 year, 85% allo	77% @ 12 yrs; older, living alone, physical/mental late effects, fatigue	BMT 2017; 52: 1436
Kurosawa	X-sec survey	N=1048, 20-64, >2 yr allo DFS	52-76% @ 5 years; female, older, PT	J Cancer Surv 2021, online
Bhatt	CIBMTR study	N=2844 childhood HCT, 1985-2010, allo	73% when 28-32 y/o; RIC/NMA, older at HCT	Cancer 2019; 125: 144
Bhatt	CIBMTR study	N=1365 YA, 2008-2015, allo	50% @ 1-3 yrs; female, HCT-CI ≥ 3 , grade III-IV acute GVHD, relapse	TCT 2021; 27: 679.e1-e8

Predictors of not RTW

- Patient factors: Female, lower education, older
- Symptoms: Fatigue, pain, cognitive dysfunction
- Co-morbidities: HCT-CI, number of hospitalizations
- Medical complications: grade III-IV acute GVHD, relapse, chronic GVHD
- Transplant variables: TBI

Kirchhoff J Cancer Surviv 2010; 4: 33
Wong Blood 2010; 115: 2508
Morrison BBMT 2016; 22: 1690
Murgaugh Cancer 2020; 126: 2174
Bhatt TCT 2021; 27: 679.e1
Kurosawa J Canc Surv 2021; online



ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org



Return-to-Work Guidelines and Programs for Post-Hematopoietic Cell Transplantation Survivors: An Initial Survey



Rachel B. Salit^{1,2,*}, Stephanie J. Lee^{1,2}, Linda J. Burns³, Bronwen E. Shaw⁴, Navneet S. Majhail⁵, Neel S. Bhatt^{1,2}, William A. Wood⁶, Karen L. Syrjala^{1,2}

¹ Fred Hutchinson Cancer Research Center, Seattle, Washington

² University of Washington School of Medicine, Seattle, Washington

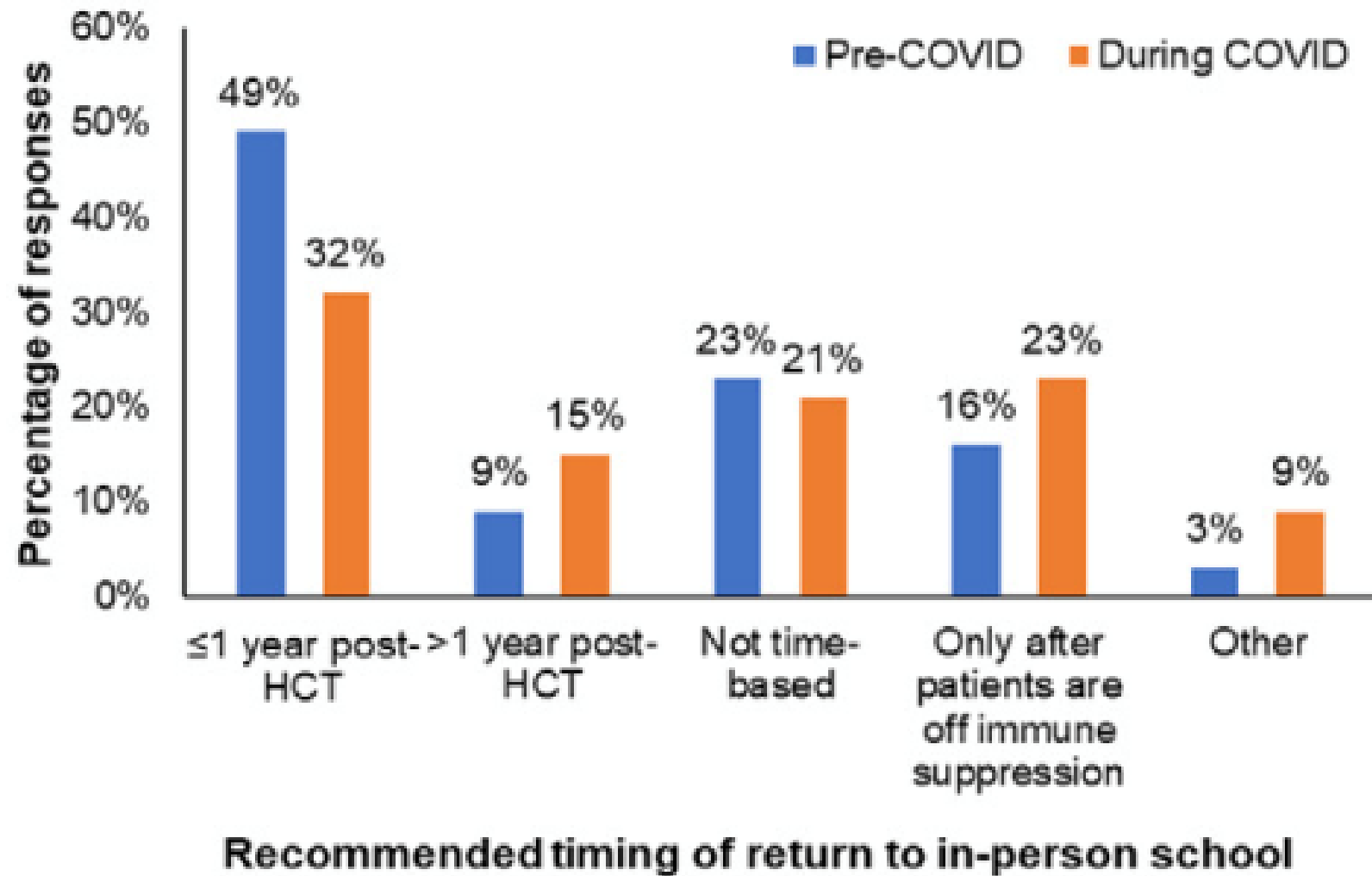
³ Transplant, Cellular Therapy, and Health Services Research, LLC, Stillwater, Minnesota

⁴ Center for International Blood and Marrow Transplant Research and Medical College of Wisconsin, Milwaukee, Wisconsin

⁵ Blood and Marrow Transplant Program, Cleveland Clinic, Cleveland Ohio

⁶ Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

- 45 transplant programs (30% response)
- 100% recommended RTW <6 mos for autos
- 4 mos - >12 mos for allos: type of job, immunosuppression
- 35% recommended gradual RTW



Causes of Disability

- Physical – strength, stamina
- Mental – depression, anxiety, PTSD
- Cognitive – executive function, memory
- Symptoms – fatigue, pain
- Co-morbidities – CVD, pulmonary, diabetes, bone health
- Risk of infections – immunosuppressed (due to chronic GVHD, medications, maintenance Rx), COVID
- Frequent medical care, hospitalization, absenteeism
- Most post-HCT disabilities are not “visible” or self-limited

Trends in HCT – Implications for disability

- Older, sicker patients can undergo HCT
 - Studies show survival benefits with HCT over non-HCT therapy
- Unclear whether “gentler” transplant approaches and better supportive care result in
 - Better overall health of the HCT survivor population
 - More people surviving in poor health

Summary

- Many people are already disabled before HCT
- Autos recover earlier and have fewer late effects than allos but their reported health looks more similar than different at 1 year – except for chronic GVHD
- There is a high burden of co-morbidities, ongoing medical care, and compromised function and QOL
 - Improves with time but plateaus at 70-80% recovery [LE, work, PROs]
 - Most disabilities are not visible or self-limited
- Only 50-80% of people return to FT/PT work/school after HCT
- Rates of post-HCT disability burden will rise as we transplant more and sicker patients
 - More maintenance treatments



THANK YOU

Questions?