Haploidentical Transplantation An Overview

ACBSCT Meeting September 2020

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A research collaboration between the National Marrow Donor Program (NMDP)/Be The Match and the Medical College of Wisconsin

Conflict of Interest

- I have no financial conflict of interest

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Distribution of Donor Types in 2019 in the U.S

	Adults	Children
HLA-matched sibling	20%	25%
HLA-haploidentical relative	20%	20%
HLA-matched/mismatched unrelated adult	55%	35%
Umbilical cord blood	5%	20%

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Courtesy CIBMTR June 2020

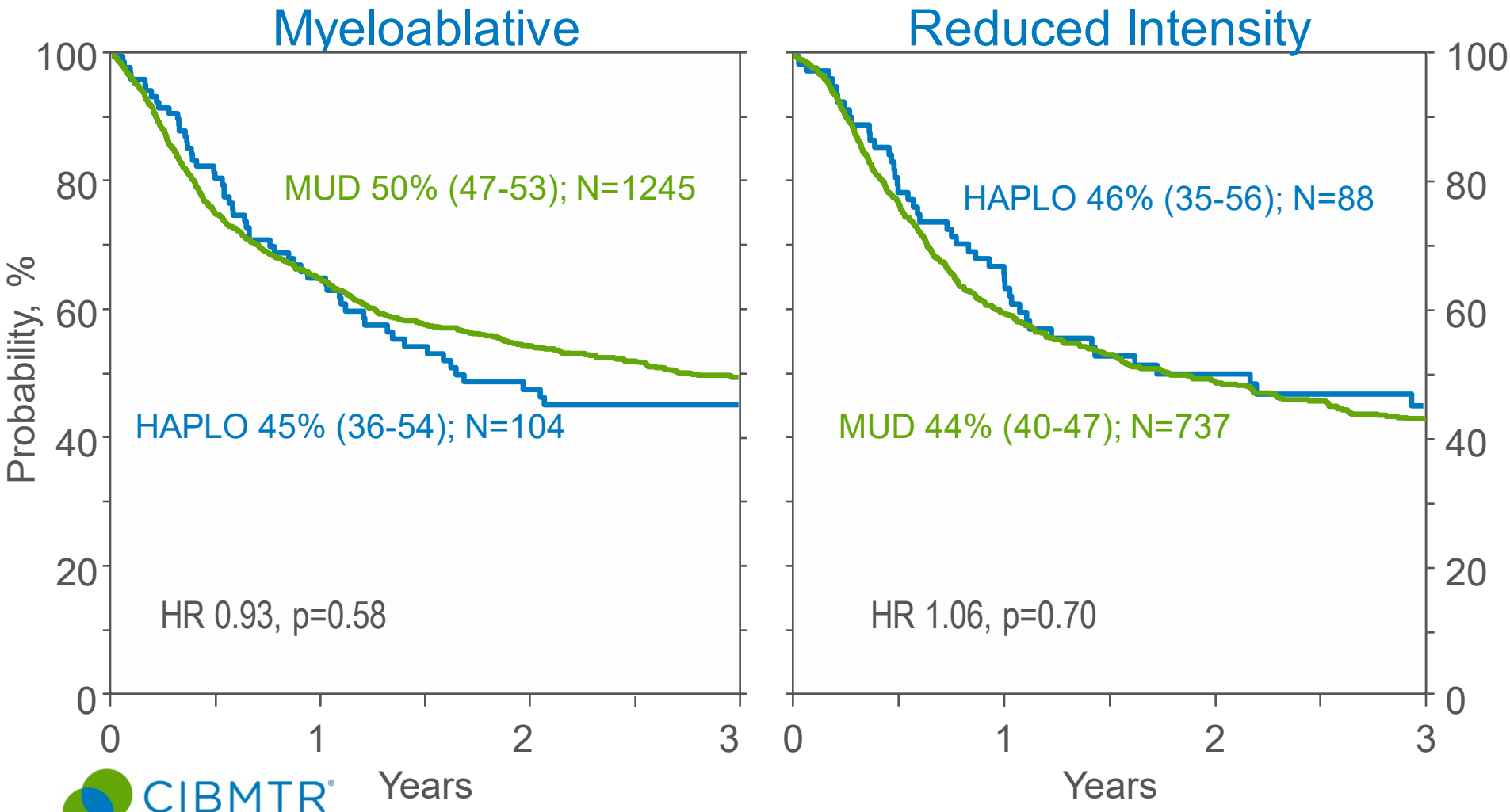
Haploidentical Relative Donor Transplants

- Increasing common approach to HCT in the US
  - Malignant and non-malignant hematologic diseases
  - Bone marrow or peripheral blood
  - GVHD prophylaxis
    - Post-transplant cyclophosphamide (PT-Cy)
  - Reduced intensity or myeloablative conditioning
    - Low dose TBI/cyclophosphamide/ATG
    - Alkylating agent/fludarabine ± ATG

Is a Haploidentical Relative Comparable to Matched Unrelated Donor?

- Donor selection varies between centers
- Some centers prioritize a haploidentical relative if a matched relative is not available
- So is a haploidentical relative comparable to a matched unrelated donor?
  - Post-transplant cyclophosphamide overcomes the HLA barrier – but to what extent?

Overall Survival Haplo vs MUD in AML



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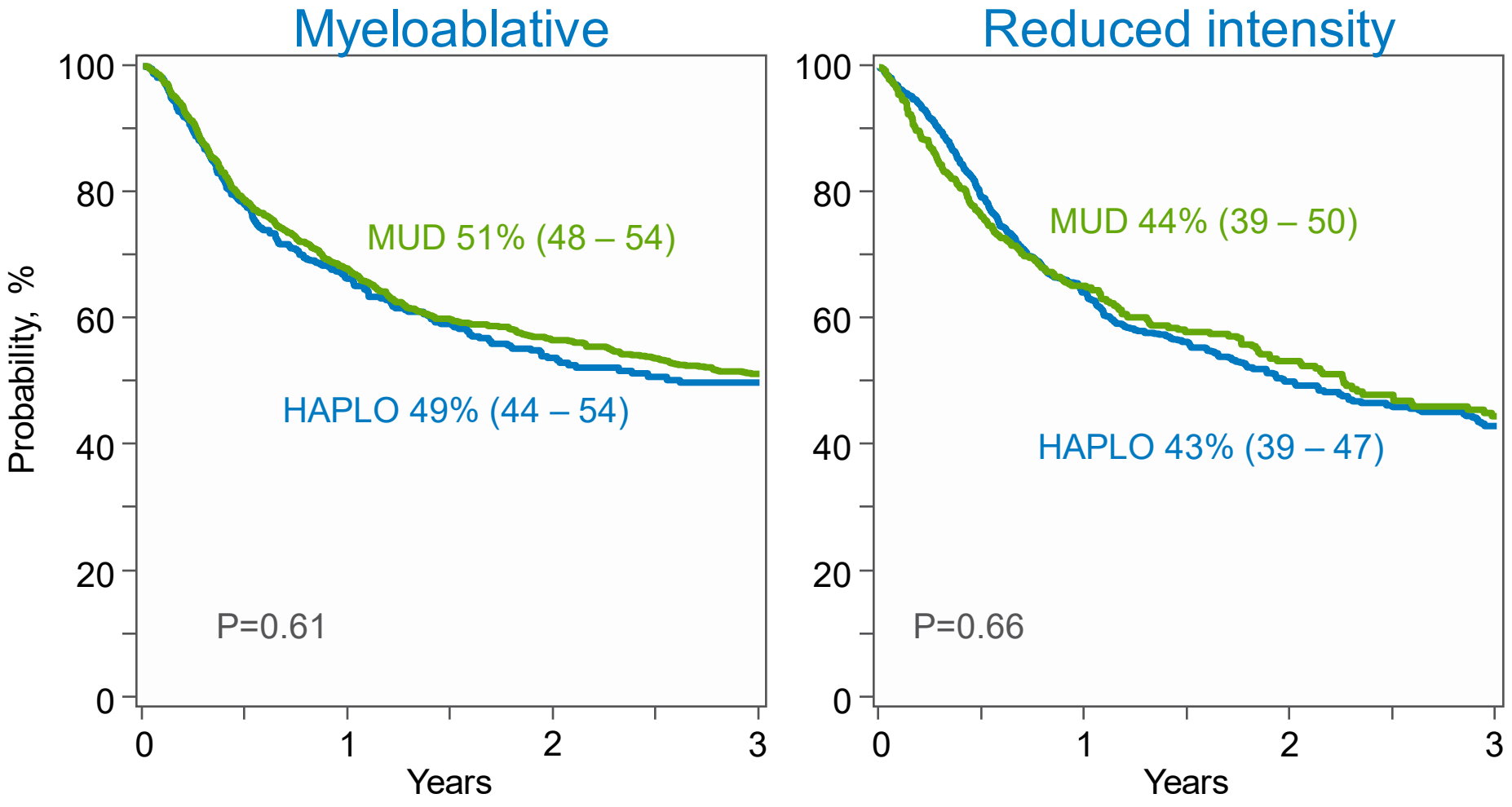
Ciurea S, Blood 2015

Overall Survival 2019: Acute Myeloid Leukemia



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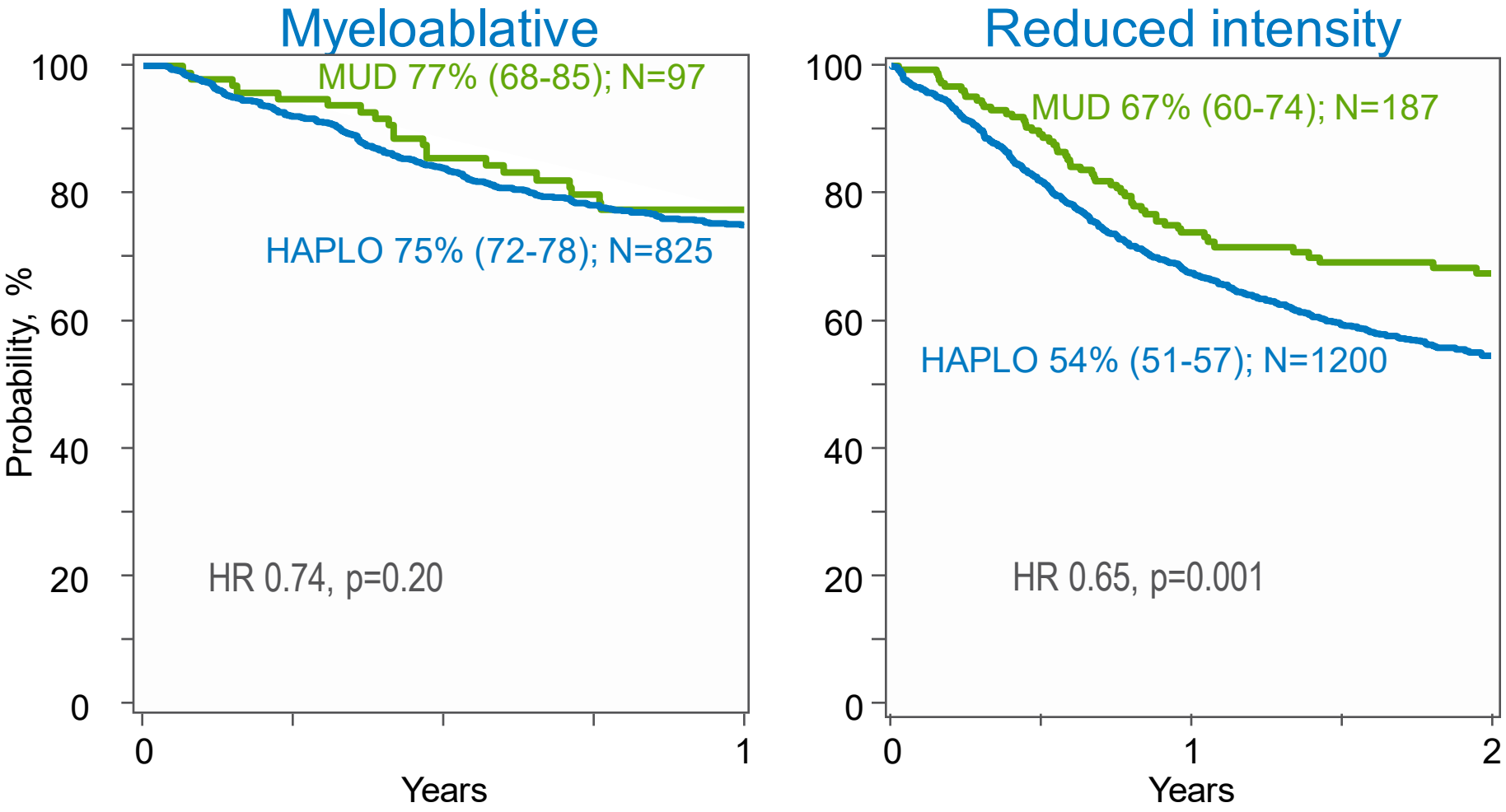
Courtesy CIBMTR February 2019

Overall Survival Haplo vs. MUD with Post-transplant Cyclophosphamide: Acute Myeloid Leukemia



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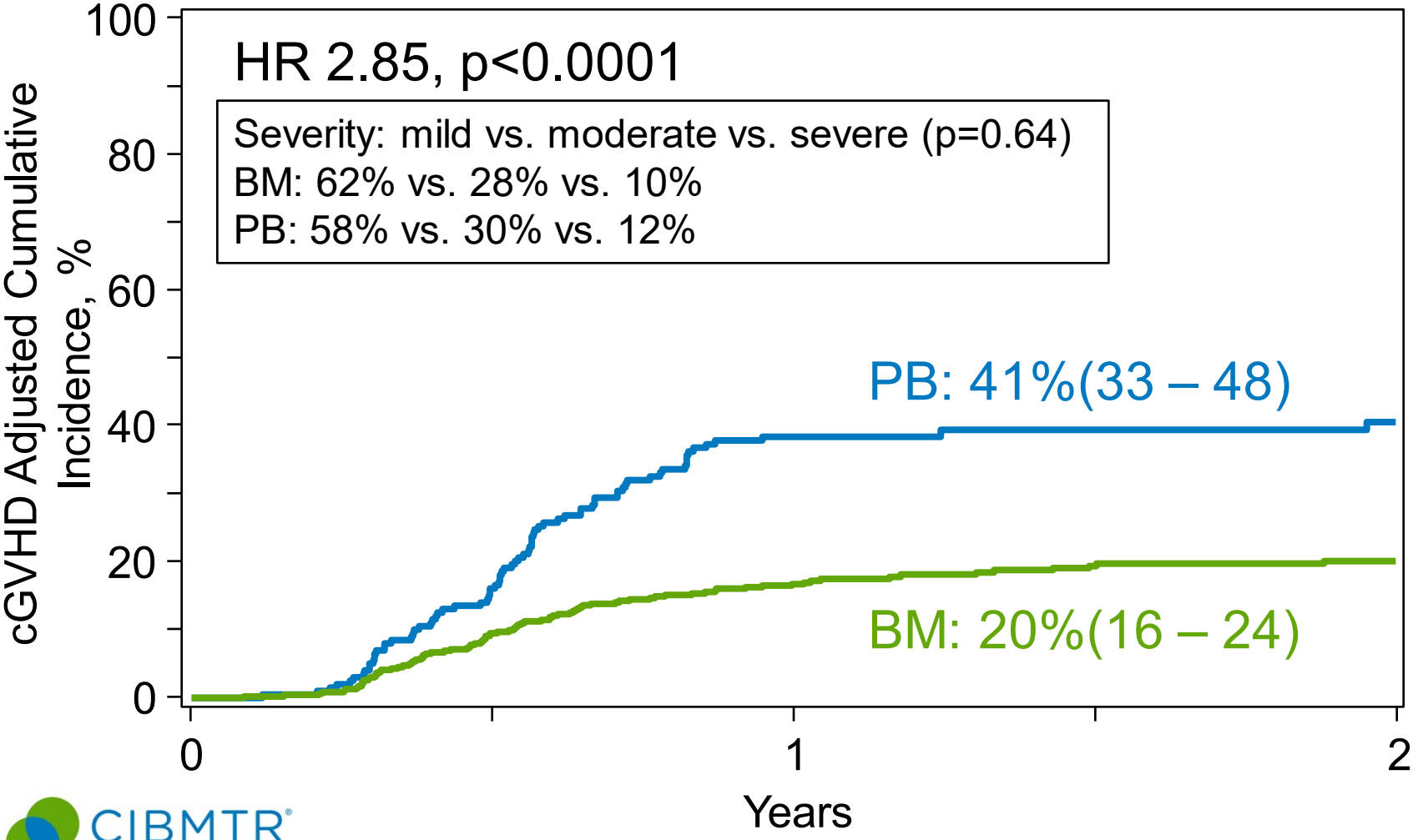
Courtesy CIBMTR July 2020

Haplo-HCT: Bone Marrow vs. Peripheral Blood Chronic Graft vs. Host Disease



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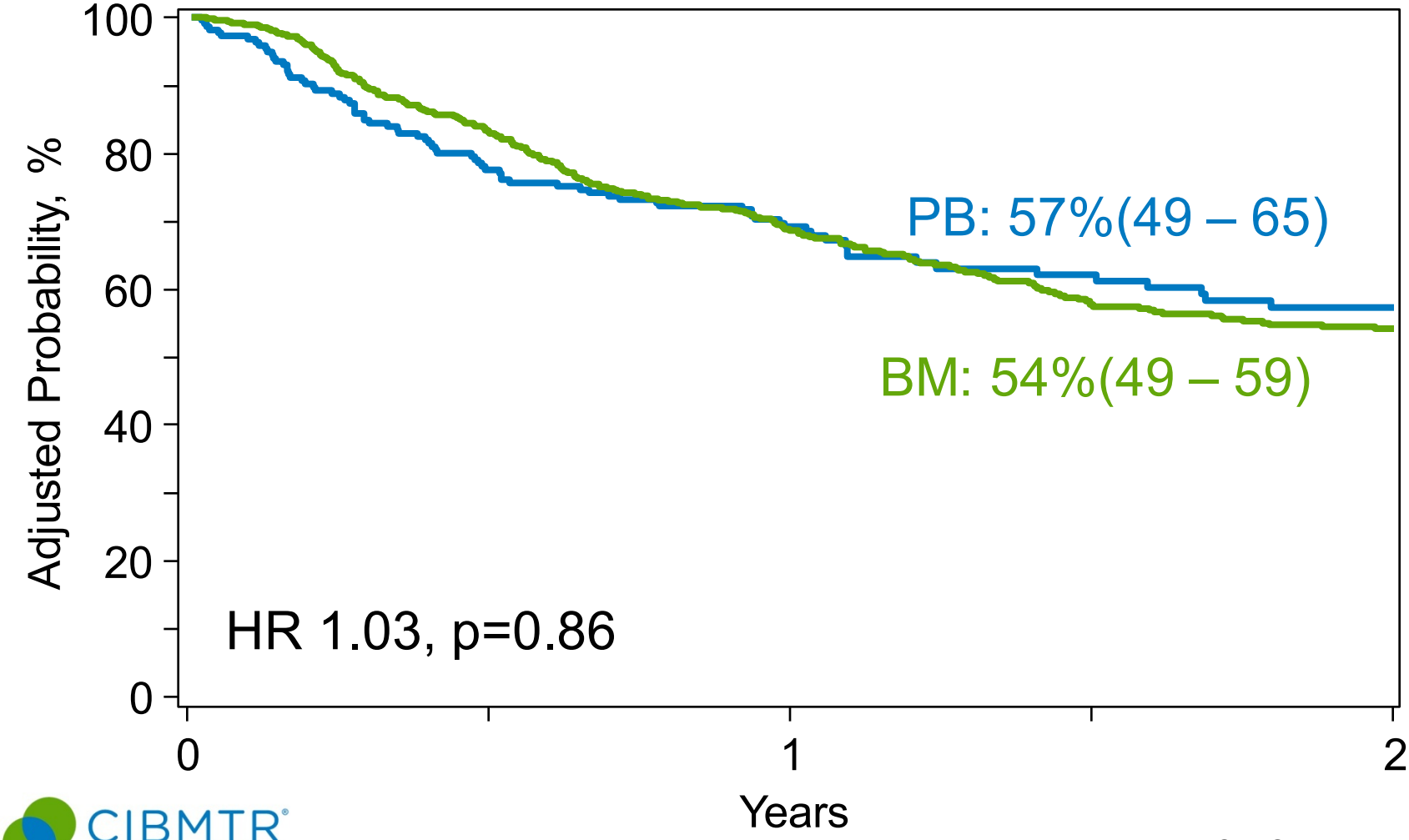
Bashey A J Clin Oncol 2016

Haplo-HCT: Bone Marrow vs. Peripheral Blood Overall Survival



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Bashey A J Clin Oncol 2016

Donor age: Adult Unrelated Donors

- Younger donors are associated with best survival
  - For every 10-year increment in donor age there is a 5.5% increase in the hazard ratio for overall mortality

- So, are younger haploidentical donors better than older haploidentical donors?
- Are there other donor characteristics to consider?

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Kollman C et al. Blood 2016

Haplo-HCT: Donor Characteristics

- Strong correlation between:
  - Recipient age and donor relationship ($r = 0.66$, $p<0.0001$)
  - Donor age and donor relationship ($r = -0.61$, $p<0.0001$)
- No correlation b/w patient and donor age ($r = 0.06$, $p=0.06$)

- Higher mortality for patients aged ≥55 years

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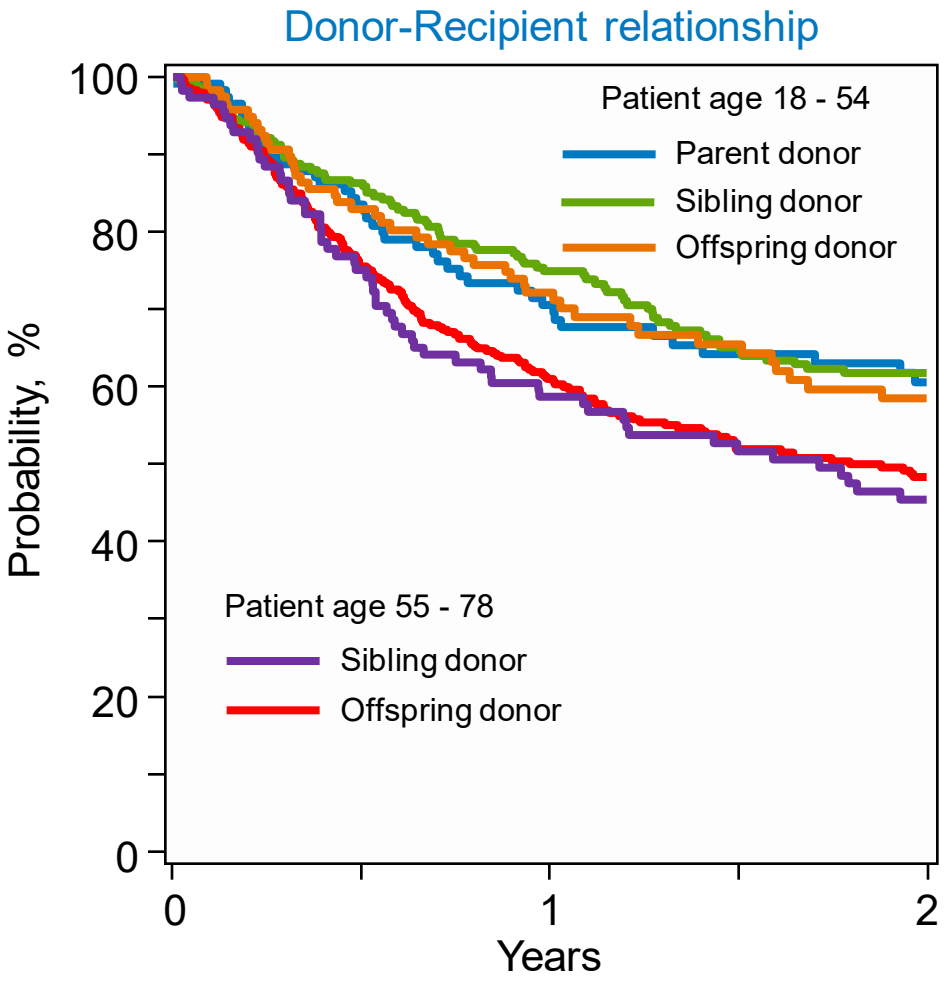
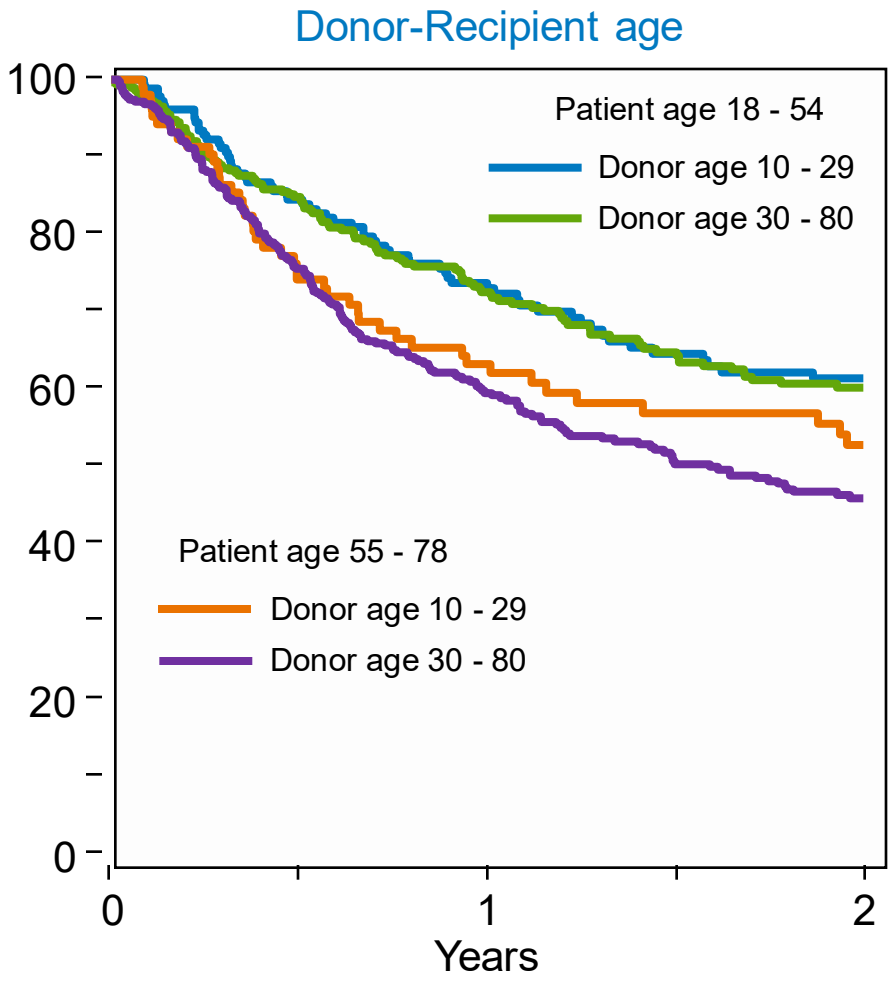
McCurdy S, Blood Adv 2018

Overall survival by donor-recipient age and relationship





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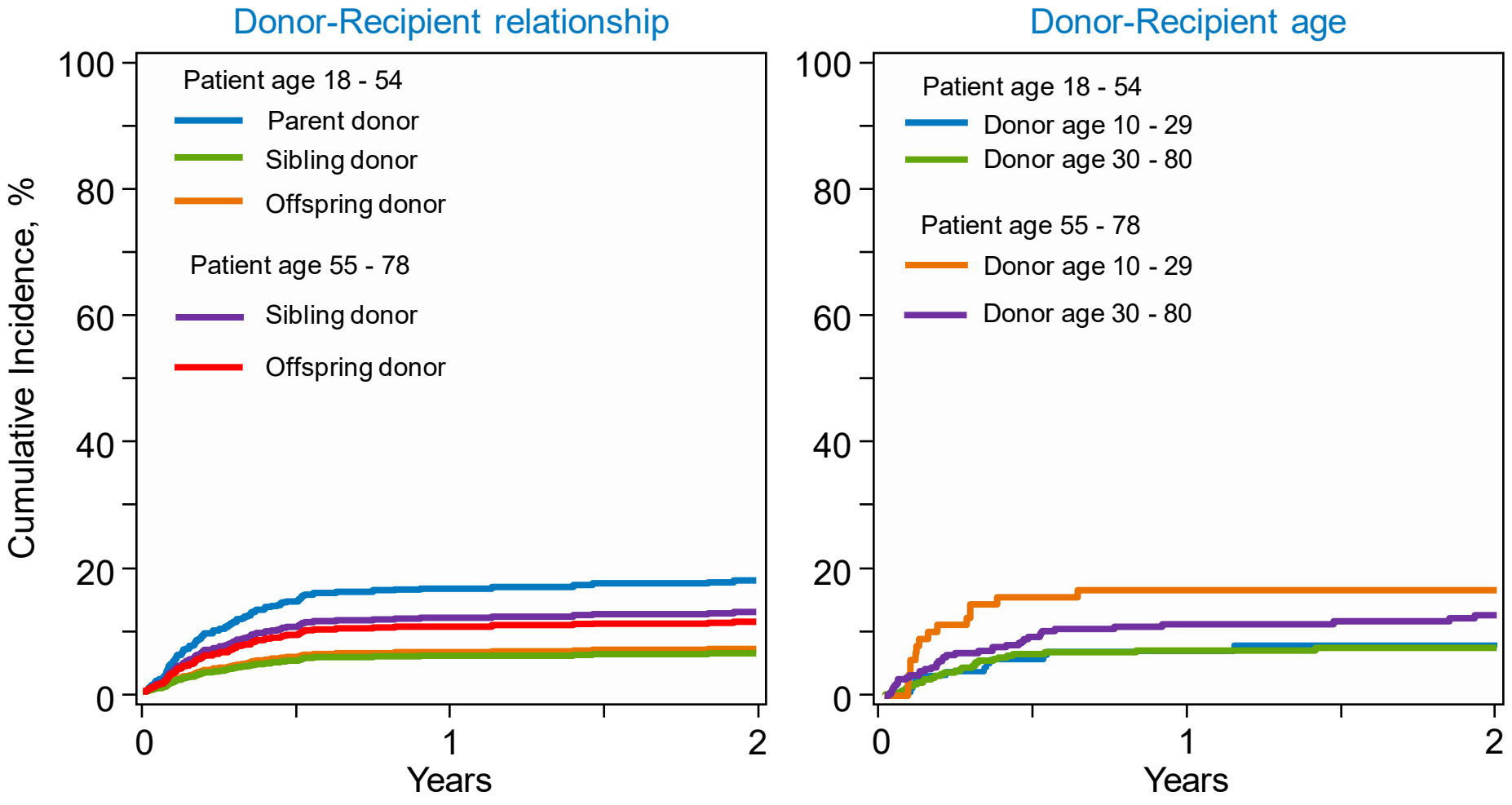
McCurdy S, Blood Adv 2018

Graft failure by donor-recipient age and relationship



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McCurdy S, Blood Adv 2018

Summary: Haplo-HCT and Donor Characteristics

- Patient age is a more important predictor for survival than donor age or donor-recipient relationship
  - Higher mortality in patients aged ≥55 years
- Avoid parents as donors: higher risk for graft failure
- Donor sex, parity, CMV serostatus, donor-recipient ABO match: not associated with outcomes

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McCurdy S, Blood Adv 2018

Summary: Haplo-HCT for Leukemia

- Haploidentical relatives are suitable alternative donors:
  - When matched sibling is not available
  - In unselected populations: similar 2-year survival to that after matched unrelated donor transplant
  - Selected populations: HLA-matched unrelated is preferred (higher survival)
    - Similarly, HLA-matched sibling preferred
  - AML is the predominant disease
- Bone marrow or peripheral blood?:
  - Higher chronic GVHD with peripheral blood
  - No difference in survival

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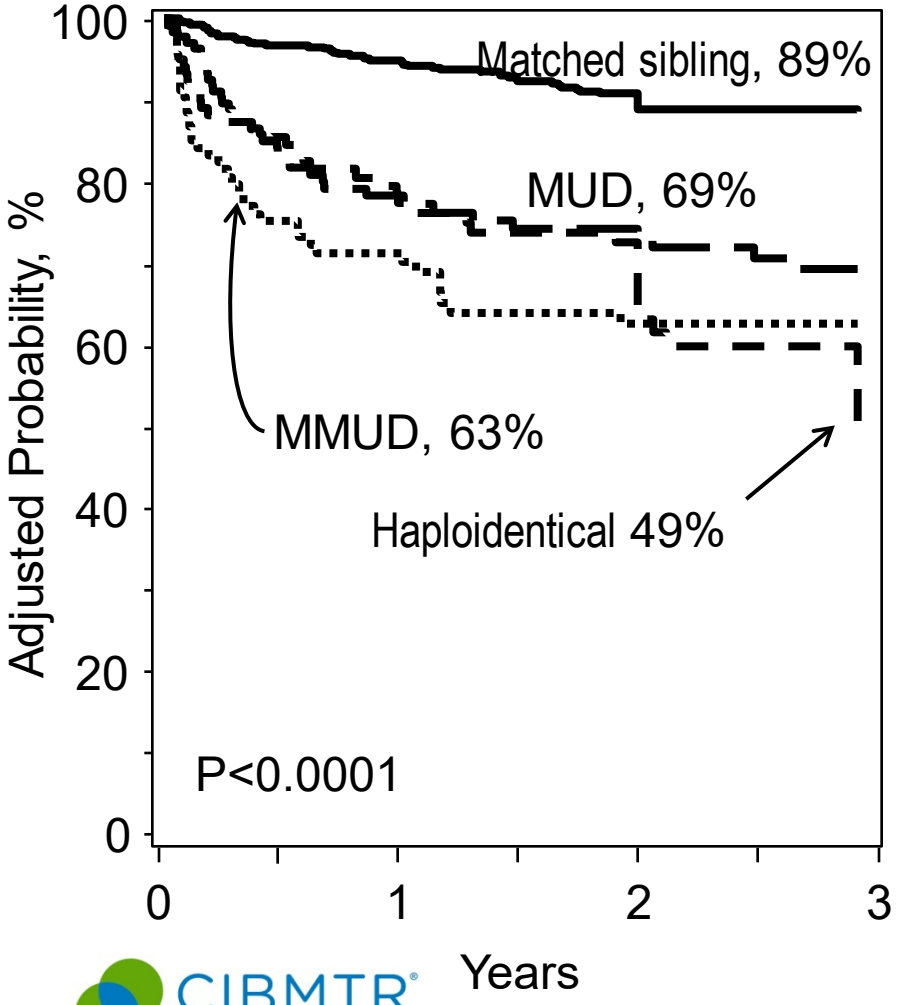
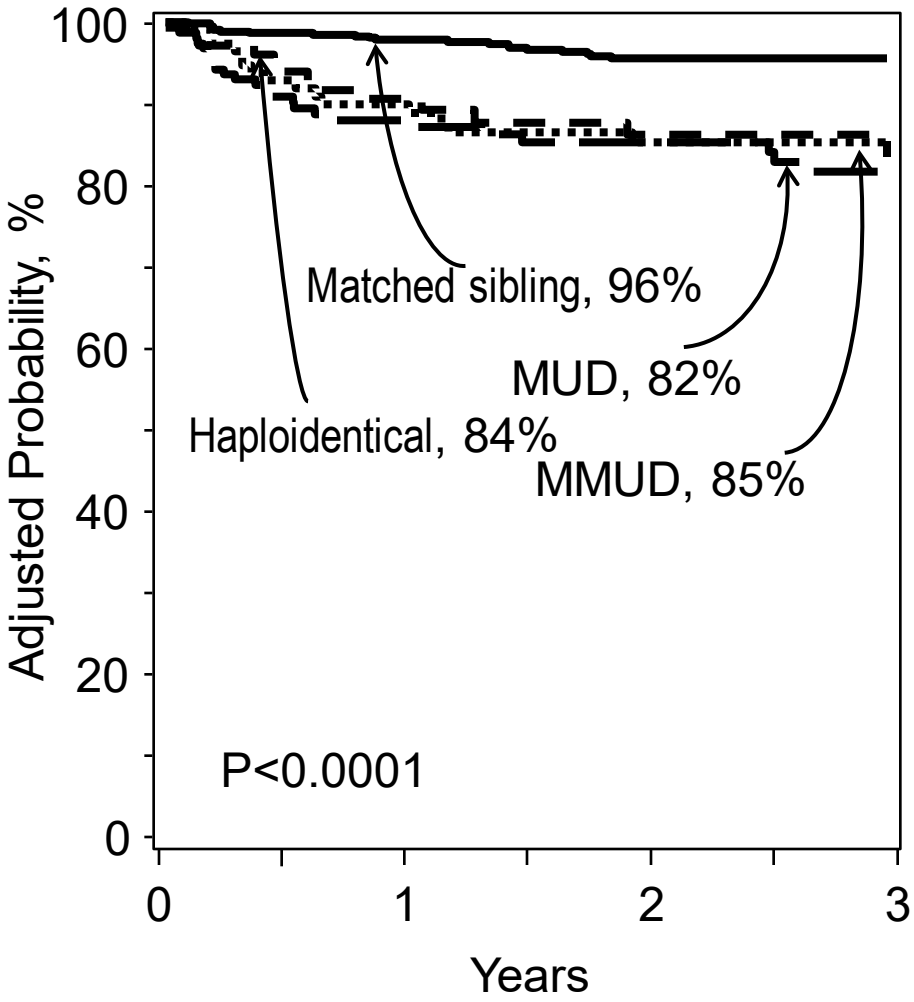
Outcomes: Allogeneic HCT for Sickle Cell Disease

Event-free Survival



Overall Survival



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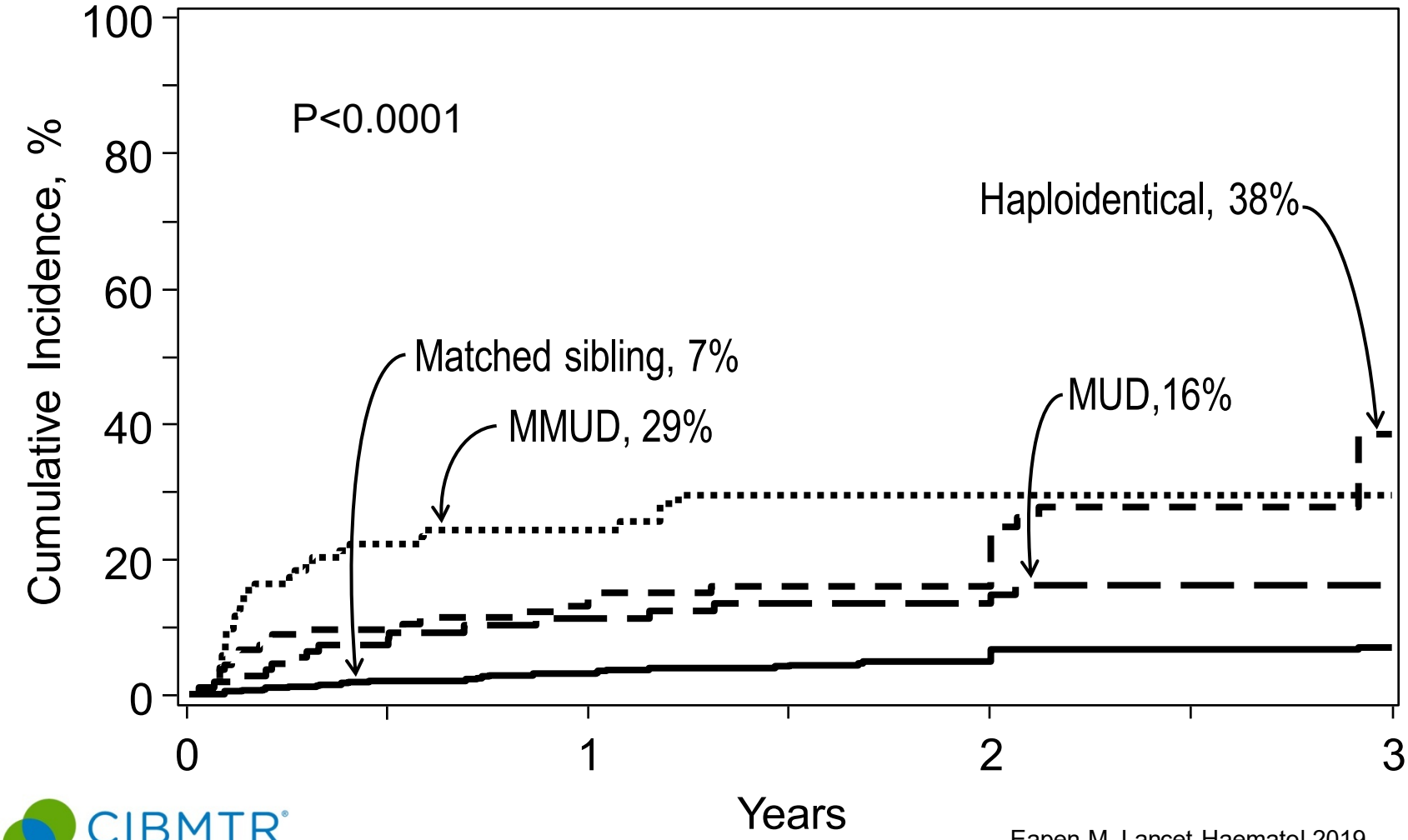
Eapen M, Lancet Haematol 2019

Graft failure: Allogeneic HCT for Sickle Cell Disease



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Eapen M, Lancet Haematol 2019

Summary: Allogeneic HCT for Sickle Cell Disease

- Event-free survival is highest in children aged <13 years and after matched sibling transplant HCT
- Mortality and graft failure higher after alternative donor HCT
- The data does not favor one alternative donor over another
  - However, higher graft failure with haploidentical and mismatched unrelated donor compared to matched unrelated donor HCT
  - Graft failure continued beyond 2 years after haploidentical donor HCT underscoring the need for continued follow-up

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Eapen M, Lancet Haematol 2019

Considerations for HCT in Sickle Cell Disease

- Deciding whether to recommend HCT for sickle cell anemia is not straight forward
- Severity of disease vary and there are several disease modifying drugs
- To assist in counselling for HCT we propose a simple risk score
  - Developed and validated in a cohort of 1425 patients
  - Risk score was developed on age at HCT and donor type

Sickle Cell Risk Group Composition

Clinical characteristic	Risk group	HR	P-value
Age ≤ 12 years Matched sibling donor	Good Score = 0	1.00	<0.0001
Age ≤ 12 years Matched unrelated donor Age ≥13 years Matched sibling donor	Intermediate Score = 1	2.52	0.043
Age ≤ 12 years Mismatched donors Age ≥13 years Alternative donors	High Score = 2, 3	7.71	<0.0001

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Brazauskas R, Blood 2020

Outcomes by Sickle Cell Risk Group

Age yrs	Age score	Donor	Donor score	Total score	EFS	Death	Graft failure
≤12	0	Matched sib	0	0	92%	2%	6%
≤12	**0**	**Haplo**	**2**	**2**	**62%**	**8%**	**30%**
≤12	0	Matched URD	1	1	83%	8%	8%
≤12	0	Mismatched URD	2	2	68%	5%	27%
≥13	1	Matched sib	0	1	87%	7%	5%
≥13	**1**	**Haplo**	**2**	**3**	**52%**	**10%**	**38%**
≥13	1	Matched URD	1	2	50%	29%	21%
≥13	1	Mismatched URD	2	3	49%	23%	28%

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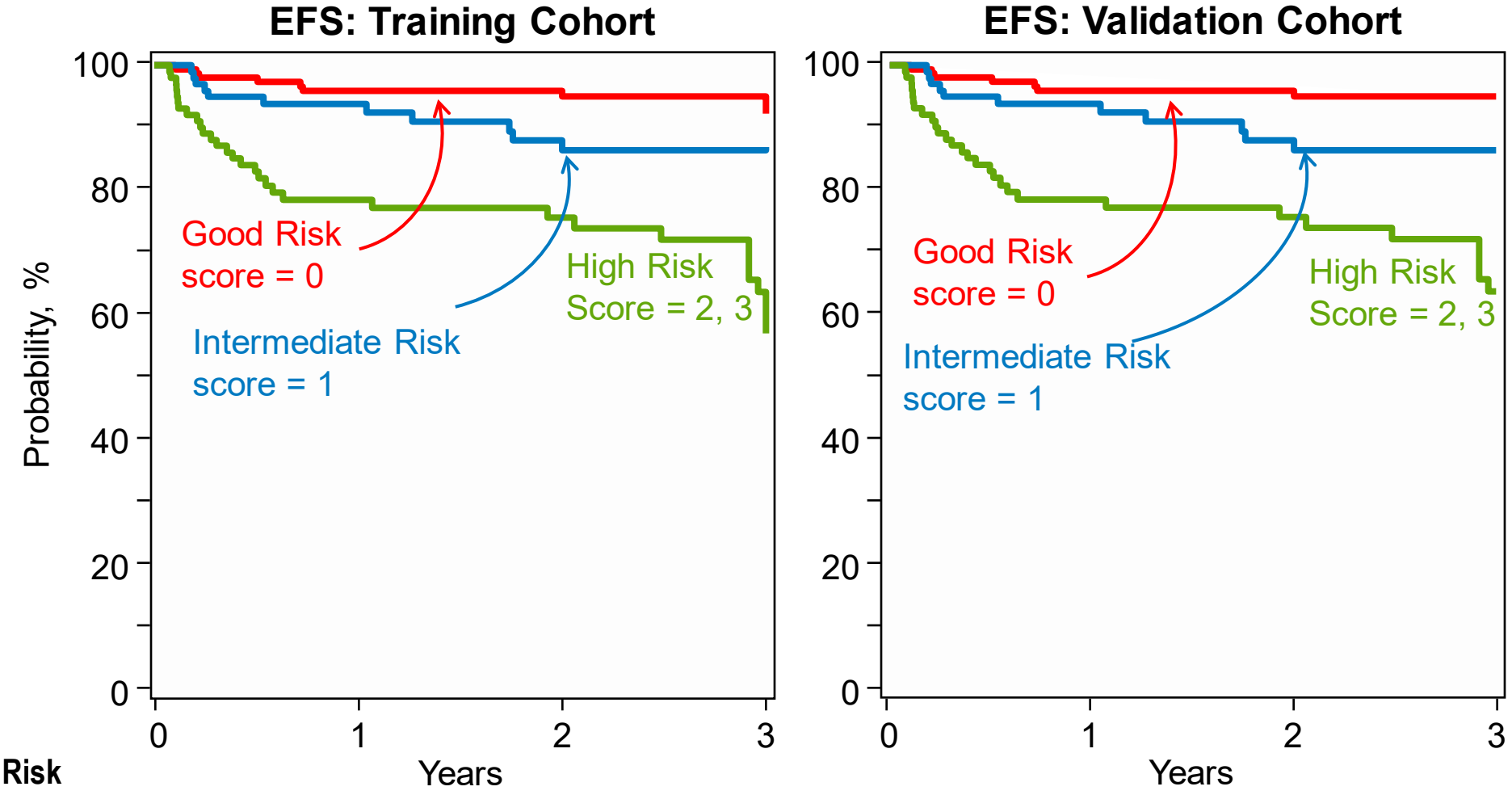
Brazauskas R, Blood 2020

EFS by Risk Score in Sickle Cell Disease



Risk Score								
0	490	394	308	241	159	121	99	72
1	293	230	175	122	98	72	49	37
2,3	287	180	130	83	98	62	46	31

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Brazauskas R, Blood 2020

Considerations for Haploidentical HCT for Sickle Cell Disease

- Event-free survival
  - 3-year EFS ~60%; 10% mortality, 30% graft failure
  - Are patients willing to accept 10% mortality relatively early after HCT?
  - Or accept ~30% will experience recurrent disease?

  - What is mortality in a patient who did not receive HCT but may be eligible for HCT?
    - General population with sickle cell disease
    - UK: median age of survival, 67 years (single center)
    - US: median age of survival, 48 years (2 centers)

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Aplastic Anemia: Haploidentical HCT

Characteristics	N = 94
Median age	23 years
Performance score 90-100	54%
HCT comorbidity index, ≥ 3	36%
Bone marrow/peripheral blood	81%/19%
Conditioning regimen	
TBI (2 Gy)/Cy/Fludarabine	75%
TBI (3 or 4 Gy)/Cy/Fludarabine	25%
GVHD prophylaxis: PT-Cy/CNI/MMF or MTX	100%
Transplant period	2014-18

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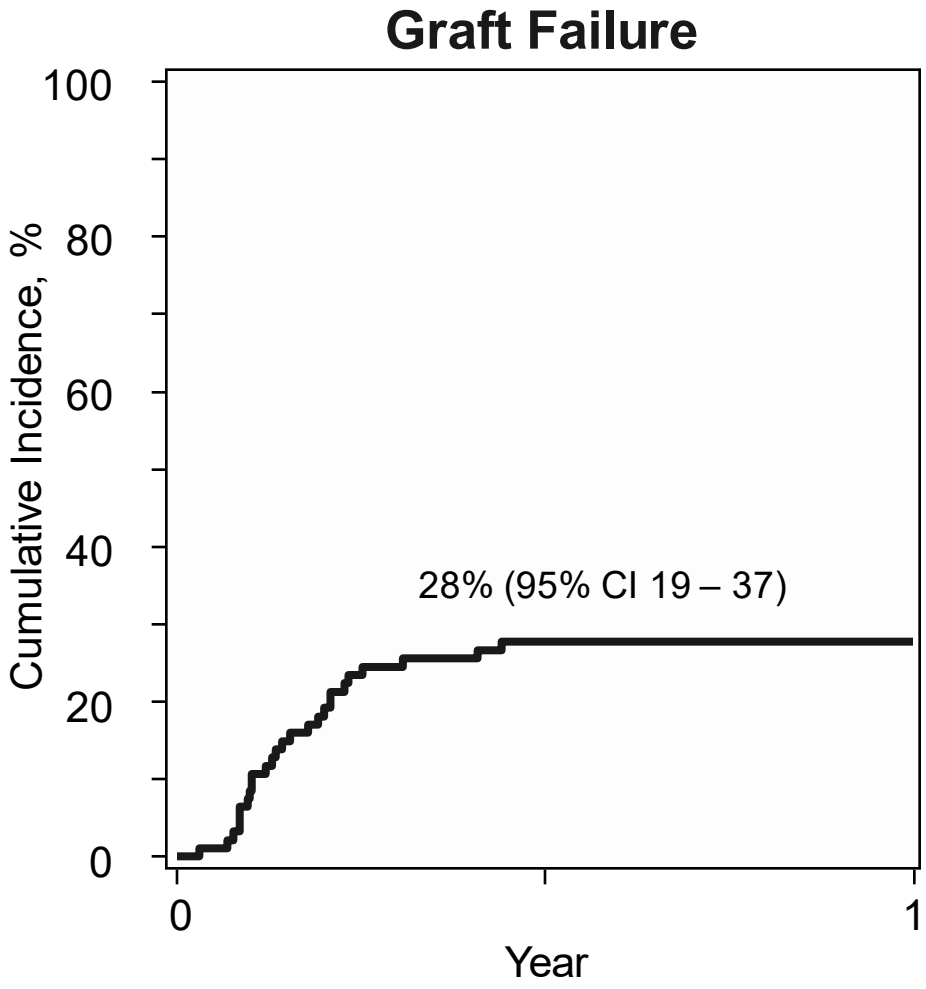
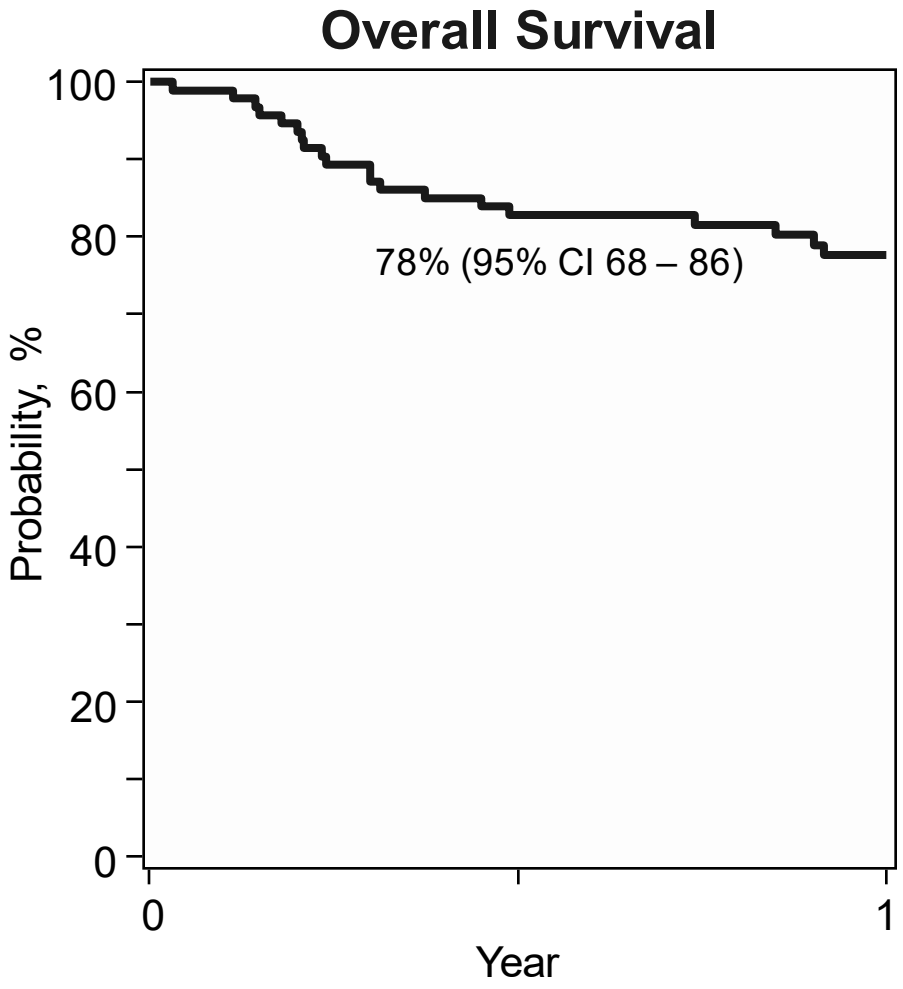
Courtesy CIBMTR September 2019

Aplastic Anemia: Haploidentical Relative HCT Outcomes





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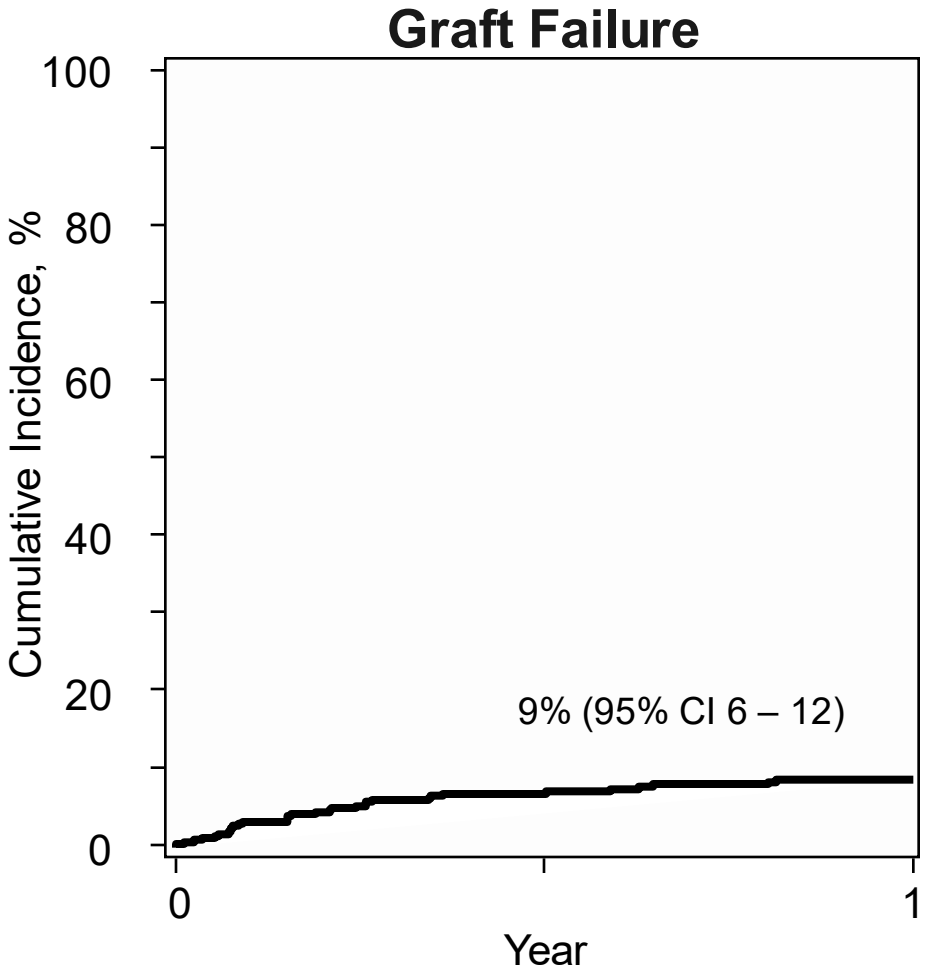
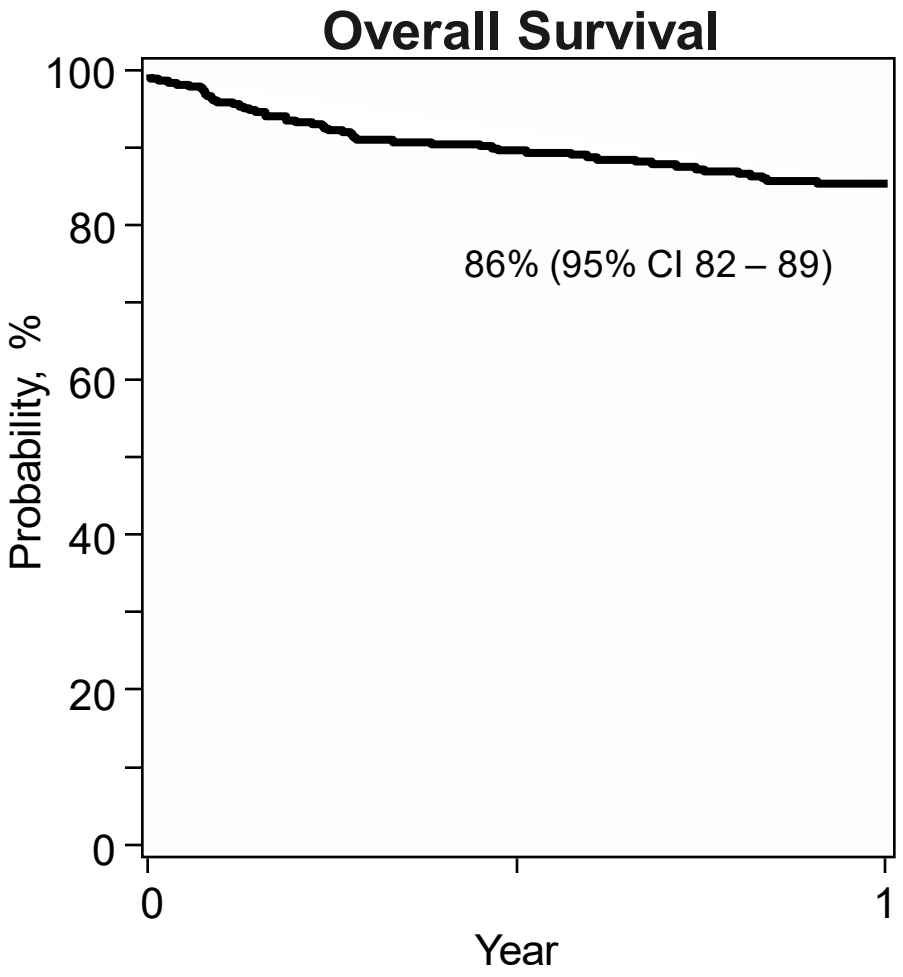
Aplastic Anemia: Matched Unrelated Donor Outcomes





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Considerations for Haploidentical HCT in Aplastic Anemia

- Aplastic Anemia
  - Data reported to transplant registry suggest HLA-matched unrelated donor is preferred to mismatched relative
  - Graft failure is an obstacle
  - Data from single institution(s) suggest survival comparable to matched unrelated donor HCT
  - BMT CTN 1502: completed accrual
    - Results expected 2022

Summary: Haplo HCT for malignant and non-malignant hematologic diseases

- Hematologic malignancy
  - Haploidentical related donors extend the donor pool making transplantation accessible to patients likely to benefit from this treatment
  - Particularly relevant for minorities who face challenges identifying HLA-matched unrelated donors
- Non-malignant hematologic diseases
  - Sickle cell disease and aplastic anemia
    - We must improve current transplant strategies to overcome graft failure after haploidentical donor HCT and overcome GVHD after unrelated donor HCT

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