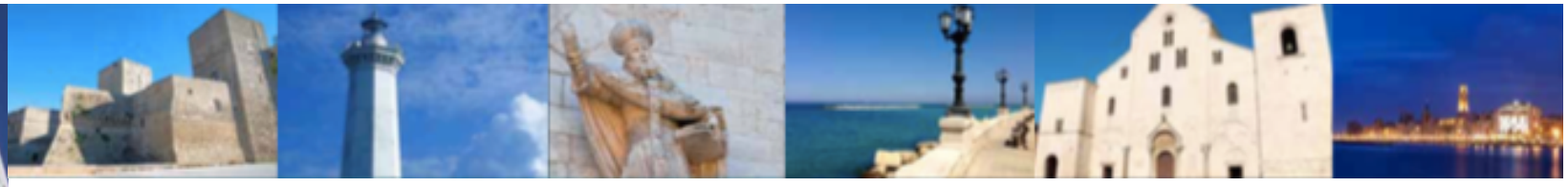


Donatore HLA identico di 60-70 anni
o
MUD giovane?

Stella Santarone
Dipartimento di Ematologia, Medicina Trasfusionale e Biotecnologie
Pescara

BMT Center Pescara

AGENDA

1. Stem Cell Donation: fatalities and severe events
2. General consideration on older age donor and hemopoietic system
3. Impact of donor age on outcome after allogeneic HCT
4. Who is the better donor: older-aged sibling vs or young MUD

Severe events in donors after allogeneic hematopoietic stem cell donation

Joerg Halter,[1] Yoshihisa Kodera,[2] Alvaro Urbano Ispizua,[3] Hildegard T. Greinix,[4] Norbert Schmitz,[5] Geneviève Favre,[1] Helen Baldomero,[6] Dietger Niederwieser,[7] Jane F. Apperley,[8] and Alois Gratwohl[1] for the European Group for Blood and Marrow Transplantation (EBMT) activity survey office

EBMT Study, 262 participating centers, retrospective, 1993-2002 and 2003-2005
First allotransplant

	No.	FATALITIES	Prevalence %
BM donation	27.760	1	0.003
PBSC donation	23.254	4	0.001
TOTAL	51.024	5	0.009

Incidence: 0.98 per 10.000 first transplants (BM 0.36 / PBSC 1.72)

Haematologica 2009;94(1):94-101

Severe events in donors after allogeneic hematopoietic stem cell donation

Joerg Halter,[1] Yoshihisa Kodera,[2] Alvaro Urbano Ispizua,[3] Hildegard T. Greinix,[4] Norbert Schmitz,[5] Geneviève Favre,[1] Helen Baldomero,[6] Dietger Niederwieser,[7] Jane F. Apperley,[8] and Alois Gratwohl[1] for the European Group for Blood and Marrow Transplantation (EBMT) activity survey office

Table 1. Characteristics of donors who died within 30 days after stem cell donation.

Donor number	Age (years)	Sex	Mode of harvest	Mobilization	Number of harvest days	Died on day	Donor-recipient relationship	Cause of death
1	38	Male	BM	n.a.	1	15	Related	Massive pulmonary embolism after diagnosis of deep vein thrombosis and pulmonary embolism on day 7. Antithrombin III deficiency was later diagnosed in the family but was unknown at the time of donation
2	67	Male	PB	G-CSF	2	29	Related	Subarachnoid hematoma on day 1. Died on day 29.
3	43	Male	PB	G-CSF	2	15	Related	Cardiac arrest (no autopsy). Risk factors: arterial hypertension, heavy smoker
4	52	Male	PB	G-CSF	2	17	Related	Cardiac arrest Risk factor: smoker
5	27	Male	PB	G-CSF	1	0	Related	Cardiac arrest after human error (see text). Resuscitation unsuccessful

Haematologica 2009;94(1):94-101

Severe events in donors after allogeneic hematopoietic stem cell donation

Joerg Halter,[1] Yoshihisa Kodera,[2] Alvaro Urbano Ispizua,[3] Hildegard T. Greinix,[4] Norbert Schmitz,[5] Geneviève Favre,[1] Helen Baldomero,[6] Dietger Niederwieser,[7] Jane F. Apperley,[8] and Alois Gratwohl[1] for the European Group for Blood and Marrow Transplantation (EBMT) activity survey office

SEVERE ADVERSE EVENTS AMONG 51,024 STEM CELL DONATIONS

	BM donations 27.760	PBSC donations 23.254
Cardiovascular*	7	11
Polmonary	1	1
Haemorrage SNC	1	2
Seizures	-	1
Splenic rupture	-	5
Unspecified	3	5
TOTAL (prevalence)	12 (0.04%)	25 (0.10%)

* Myocardial infarction, cardiac arrest, arrhytmia, severe hypertension, stroke

Haematologica 2009;94(1):94-101

GENERAL CONSIDERATION

- The era of RIC-HSCT, with its emphasis on older patients, has created new challenges in the management of what is now an older related stem cell donor population

- These donors are now on average no less than 10 years older than in the mid-90s. Donors over 70 yrs of age are no longer isolated or exceptional cases

- They may still be considered eligible for donation but many of them, based on the older age and their medical history, may no longer fully qualify as " healthy" or "normal"

GENERAL CONSIDERATION

- The older donor, the more likely that hematologic abnormalities, comorbidities and treated malignancies will complicate the picture
- Assessing the risk-benefit ratio for both donor and recipient can now be more challenging the ever
- These age-related developments should not necessarily disqualify them, but should prompt stem cell transplant physicians to pursue a more careful assessment of the risk-benefit ratio for both donor and recipient

IT IS A BRAVE NEW WORLD FOR RELATED STEM CELL DONORS

OPEN QUESTIONS

1. Are older SC donors hematologically “normal”?
2. How old and how many are related donors currently?
3. When exactly does a SC donor become older?
4. Should there be an upper age limit for normal related donors?
5. Do older donors mobilize PBSCS more poorly, and if so, why?
6. Older donors are likely to have more comorbidities. What impact (if any) do these have?
7. How do these older donors tolerate the donation process?
8. Some of these older donors are cancer survivors. Does it matter?

Anderlini P et al. BMT 2017;52:15-19

OPEN QUESTIONS

1. **Are older SC donors hematologically “normal”?**
2. How old and how many are related donors currently?
3. When exactly does a SC donor become older?
4. Should there be an upper age limit for normal related donors?
5. Do older donors mobilize PBSCS more poorly, and if so, why?
6. Older donors are likely to have more comorbidities. What impact (if any) do these have?
7. How do these older donors tolerate the donation process?
8. Some of these older donors are cancer survivors. Does it matter?

ARE OLDER STEM CELL DONORS HEMATOLOGICALLY “NORMAL”?

- Aging has a profound impact on the hematopoietic as well as immune system particularly on T cells
- Somatic mutations detectable by DNA sequencing were rare under the age of 40 yrs, but became far more common in older age groups, particularly after the age of 60 yrs
- The presence of such mutations was linked to a higher risk of hematologic cancers and an increase in all-cause mortality
- Normal aging has been linked with the progressive shortening of telomeres in HSCs
- Telomere shortening or dysfunction can affect the longevity and self-renewal capacity of HSCs

OPEN QUESTIONS

1. Are older SC donors hematologically “normal”?
2. How old and how many are related donors currently?
3. When exactly does a SC donor become older?
4. Should there be an upper age limit for normal related donors?
5. Do older donors mobilize PBSCS more poorly, and if so, why?
6. Older donors are likely to have more comorbidities. What impact (if any) do these have?
7. How do these older donors tolerate the donation process?
8. Some of these older donors are cancer survivors. Does it matter?

HOW OLD AND HOW MANY ARE RELATED DONORS CURRENTLY?

		Related donors	Median age	51-60 yrs	> 60 yrs
Related Donor Safety Study	USA 2010-14	1680	48 (0-79)	28%	15%
MD Anderson Cancer Center	USA 2014-15		51 (12-75)		24%

OPEN QUESTIONS

1. Are older SC donors hematologically “normal”?
2. How old and how many are related donors currently?
3. When exactly does a SC donor become older?
4. Should there be an upper age limit for normal related donors?
5. Do older donors mobilize PBSCS more poorly, and if so, why?
6. Older donors are likely to have more comorbidities. What impact (if any) do these have?
7. How do these older donors tolerate the donation process?
8. Some of these older donors are cancer survivors. Does it matter?

WHEN EXACTLY DOES A STEM CELL DONOR BECOME “OLDER”?

- Older was defined as 50-75 years of age
- Alternatively one could use the cutoff age of 60 yrs (ineligible→ unrelated donor registries)
- Establishing some kind of age cutoff if agreed upon could be used to prompt appropriate referrals for the workup of these older donors

OPEN QUESTIONS

1. Are older SC donors hematologically “normal”?
2. How old and how many are related donors currently?
3. When exactly does a SC donor become older?
4. Should there be an upper age limit for normal related donors?
5. Do older donors mobilize PBSCS more poorly, and if so, why?
6. Older donors are likely to have more comorbidities. What impact (if any) do these have?
7. How do these older donors tolerate the donation process?
8. Some of these older donors are cancer survivors. Does it matter?

SHOULD THERE BE AN UPPER AGE LIMIT FOR NORMAL RELATED DONORS?

- Most transplanters will admit to a higher level of anxiety and nervousness (as well as taking a more cautious approach) when dealing with related donors in (60-70) , particularly if they have multiple and/or significant comorbidities

- It goes without saying that decisions about donor eligibility (or lack of) should not be based on age alone

OPEN QUESTIONS

1. Are older SC donors hematologically “normal”?
2. How old and how many are related donors currently?
3. When exactly does a SC donor become older?
4. Should there be an upper age limit for normal related donors?
5. Do older donors mobilize PBSCS more poorly, and if so, why?
6. Older donors are likely to have more comorbidities. What impact (if any) do these have?
7. How do these older donors tolerate the donation process?
8. Some of these older donors are cancer survivors. Does it matter?

DO OLDER DONORS MOBILIZE PBSCS MORE POORLY, AND IF SO, WHY?

- The older the donor, the more likely that PBSC collection will be selected in lieu of marrow harvesting
- Older donors do not mobilize PBSCs as efficiently as younger ones
- Experience with PLERIXAFOR is limited, its use should be preferably be restricted to clinical trials

OPEN QUESTIONS

1. Are older SC donors hematologically “normal”?
2. How old and how many are related donors currently?
3. When exactly does a SC donor become older?
4. Should there be an upper age limit for normal related donors?
5. Do older donors mobilize PBSCS more poorly, and if so, why?
6. Older donors are likely to have more comorbidities. What impact (if any) do these have?
7. How do these older donors tolerate the donation process?
8. Some of these older donors are cancer survivors. Does it matter?

OLDER DONORS ARE LIKELY TO HAVE MORE COMORBIDITIES. WHAT IMPACT (IF ANY) DO THESE HAVE?

- Data on this topic are very “sketchy”
- The term “comorbidity” should be reserved to patients, but it can be practical and useful when applied to donors as well
- Ideally the CoMorbidity-Age Index could be applied to donors, to assess the risk of donation-associated morbidity and mortality

OPEN QUESTIONS

1. Are older SC donors hematologically “normal”?
2. How old and how many are related donors currently?
3. When exactly does a SC donor become older?
4. Should there be an upper age limit for normal related donors?
5. Do older donors mobilize PBSCS more poorly, and if so, why?
6. Older donors are likely to have more comorbidities. What impact (if any) do these have?
7. How do these older donors tolerate the donation process?
8. Some of these older donors are cancer survivors. Does it matter?

HOW DO THESE OLDER DONORS TOLERATE THE DONATION PROCESS?

- This question has been the focus of the recently completed RDSafe Study (unrelated donors – *only up to age 60yr*s- were used as comparators in this project)

- Initial results suggest that older (≥ 60yrs) donors have high rates of baseline and donation-related pain and slow recovery

- It has been shown that older age in associated with a higher chance of requiring more than one day of collection and this can clearly affect the tolerability of the procedure

OPEN QUESTIONS

1. Are older SC donors hematologically “normal”?
2. How old and how many are related donors currently?
3. When exactly does a SC donor become older?
4. Should there be an upper age limit for normal related donors?
5. Do older donors mobilize PBSCS more poorly, and if so, why?
6. Older donors are likely to have more comorbidities. What impact (if any) do these have?
7. How do these older donors tolerate the donation process?
8. Some of these older donors are cancer survivors. Does it matter?

SOME OF THESE OLDER DONORS ARE CANCER SURVIVORS. DOES IT MATTER?

- Cancer survivors will have been exposed to chemotherapy or hormonal therapy as well

- A commonly adopted (but totally arbitrary) rule of thumbs is to allow donors with prior malignancies (except resected basal cell carcinoma or treated carcinoma in situ) provided they have been cancer free for a minimum of 5 yrs

- However, selected cases may be approached differently, depending on the expected risk of recurrence as well the availability (or lack of) of alternative donors

Supplemento ordinario alla "Gazzetta Ufficiale„ n. 300 del 28 dicembre 2015 - Serie generale

Spediz. abb. post. - art. 1, comma 1
Legge 27-02-2004, n. 46 - Filiale di Roma

GAZZETTA UFFICIALE

DELLA REPUBBLICA ITALIANA

PARTE PRIMA **Roma - Lunedì, 28 dicembre 2015** SI PUBBLICA TUTTI I GIORNI NON FESTIVI

DIREZIONE E REDAZIONE PRESSO IL MINISTERO DELLA GIUSTIZIA - UFFICIO PUBBLICAZIONE LEGGI E DECRETI - VIA ARENULA, 70 - 00186 ROMA
AMMINISTRAZIONE PRESSO L'ISTITUTO POLIGRAFICO E ZECCA DELLO STATO - VIA SALARIA, 691 - 00138 ROMA - CENTRALINO 06-85081 - LIBRERIA DELLO STATO
PIAZZA G. VERDI, 1 - 00198 ROMA

A.1 Criteri di esclusione permanente del donatore di sangue ed emocomponenti (a protezione della salute del donatore)

Il donatore affetto o precedentemente affetto da una delle sotto elencate patologie deve essere giudicato permanentemente non idoneo alla donazione di sangue o di emocomponenti.

1	Neoplasie	Sono esclusi tutti i soggetti con storia di neoplasie maligne, neoplasie ematologiche, neoplasie associate a condizioni viremiche. Possono essere accettati donatori con storia di carcinoma basocellulare o carcinoma in situ della cervice uterina dopo la rimozione della neoplasia.

Donatore HLA identico di
60-70 anni o MUD giovane?

THAT'S THE QUESTION

Shakespeare W. Amleto 1601: Atto III, Scena I

IMPACT OF DONOR AGE ON OUTCOME AFTER ALLOGENEIC HCT

Does the increasing age of donor hematopoietic cells impaired their ability to repopulate the recipient hematopoietic niche, resulting in a delay of neutrophil and platelet recoveries?

Does the aged stem cells increased the risk of post-transplantation clonal disorders?

Does the grafts from older donors adversely affected long-term transplantation-related outcomes apart from relapse of the underlying disease?

Rezvani AR, … Storb R. BBMT 2015;21:105-112

IMPACT OF DONOR AGE ON OUTCOME AFTER ALLOGENEIC HCT

- Retrospective, single center study (Seattle, 1999-2009);
- STUDY POPULATION: 1541 patients

	No.	RELATED DONOR < 60	UNRELATED <60	RELATED DONOR ≥ 60
MAC	1174	545	569	60
RIC	367	104	198	65

Rezvani AR, … Storb R. BBMT 2015;21:105-112

IMPACT OF DONOR AGE ON OUTCOME AFTER ALLOGENEIC HCT

AIMS

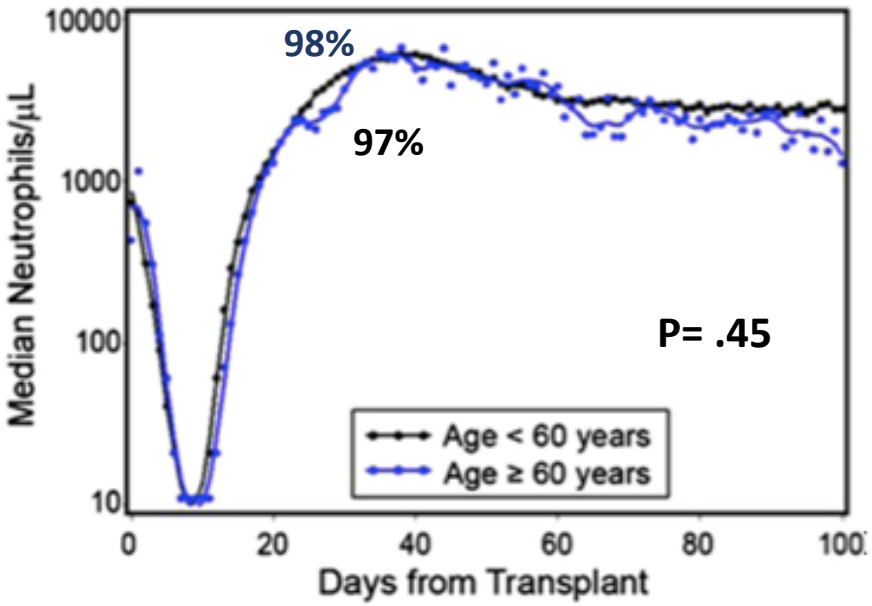
- The impact of donor age on the tempo of engraftment
- The development of clonal disorders and acute and chronic GVHD
- The 5-year nonrelapse mortality (NRM)

Rezvani AR, … Storb R. BBMT 2015;21:105-112

ENGRAFTMENT BY DONOR AGE < 60 yrs OR ≥ 60 yrs

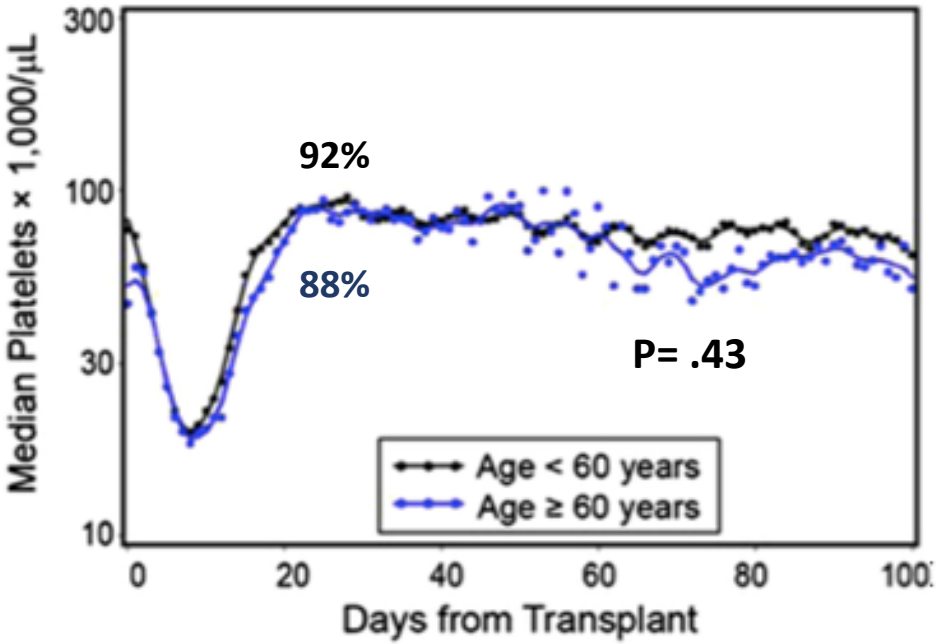
MAC Patients

NEUTROPHILS



Time to engraftment + 1.7 days ± .5 with older donors
(P= .001)

PLATELET

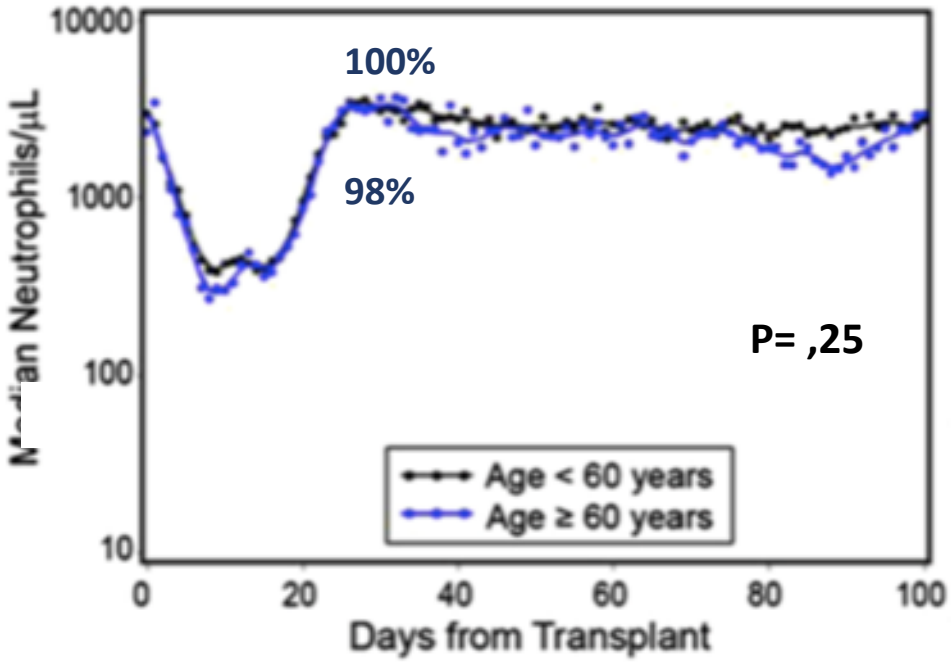


Time to engraftment + .2 days ± 1.3 with older donors
(P= .65)

ENGRAFTMENT BY DONOR AGE < 60 yrs OR ≥ 60 yrs

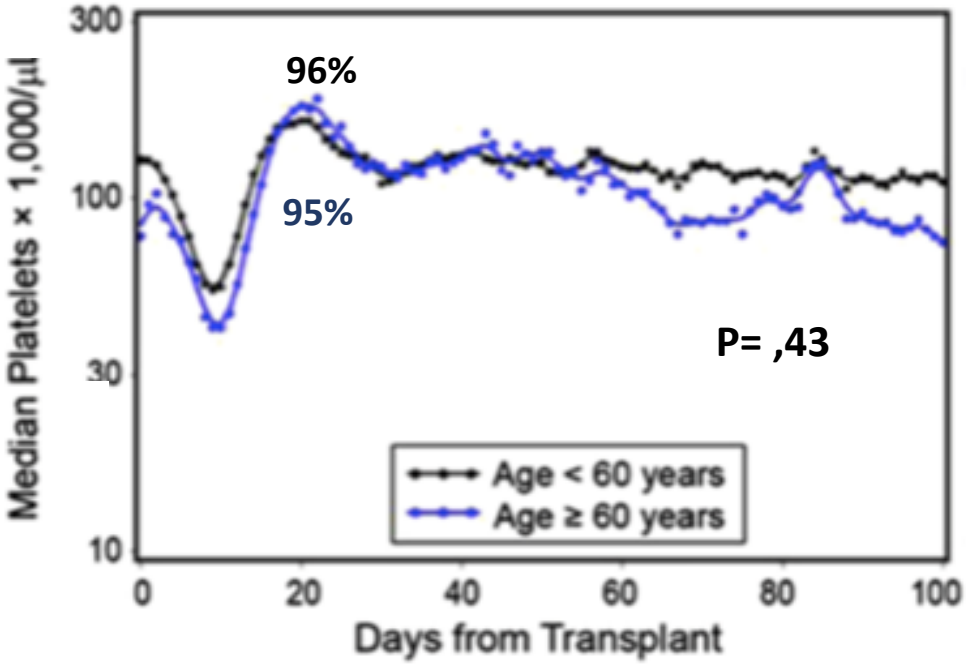
RIC Patients

NEUTROPHILS



Time to engraftment + .2 days + .7 with older donors
(P= .81)

PLATELET



Time to engraftment + .7 days + 1.1 with older donors
(P= .56)

Multivariate Regression Analysis of Patient and Transplantation Characteristics in relation to time engraftment

Myeloablative Patients

	Neutrophils (n = 935)		Platelets (n = 860)	
	Effect, d	*P*	Effect, d	*P*
Donor ≥60 yr	+1.3	.04	+.7	.65
$CD34^+$ cell dose, per log	−2.8	<.0001	−6.9	<.0001
TBI	−.2	.39	−.7	.28
Unrelated donor	−.1	.79	+1.9	.006
Male	+.2	.55	+1.3	.11
Ideal body weight, per 10 kg	+.1	.66	−.1	.65
Patient CMV^+	+.1	.72	+.2	.75
Donor CMV^+	+.2	.48	+.2	.72

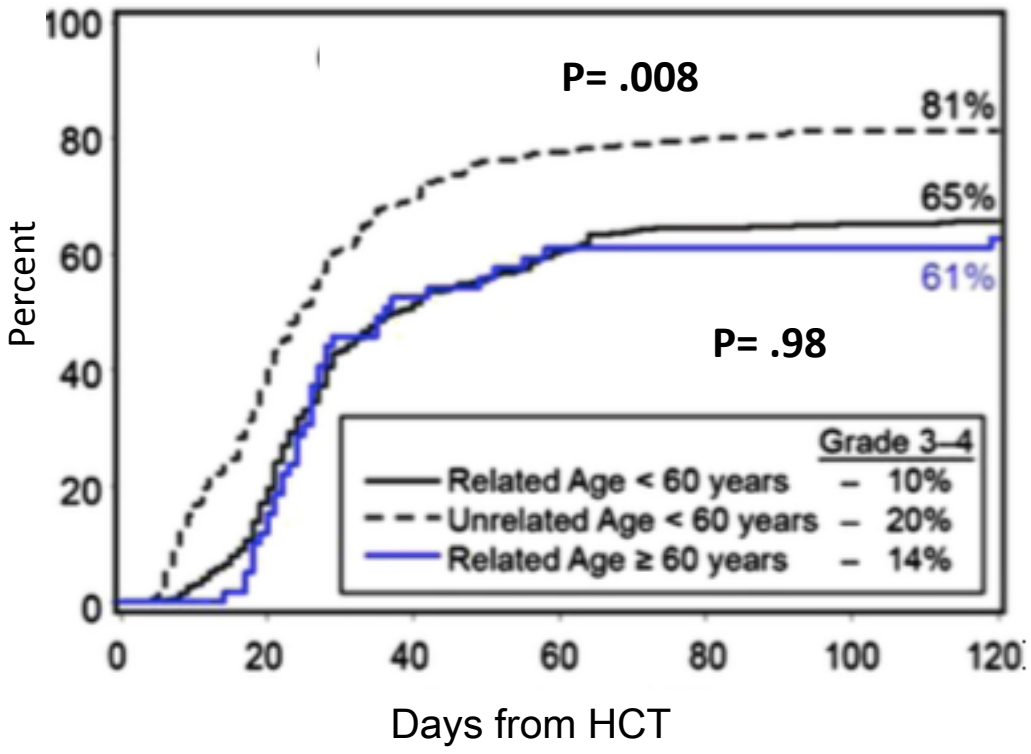
Nonmyeloablative Patients

	Neutrophils (n = 317)		Platelets (n = 310)	
	Effect, d	*P*	Effect (days)	*P*
Donor ≥60 yr	+.6	.51	−2.3	.14
$CD34^+$ cell dose, per log	−3.1	.01	−4.0	.05
Unrelated donor	+.8	.30	−3.9	.001
Male	+.4	.63	+.8	.52
Ideal body weight, per 10 kg	−.2	.46	−.3	.60
Patient CMV^+	+1.1	.08	+1.1	.28
Donor CMV^+	−1.1	.10	+.5	.66

GRAFT versus HOST DISEASE

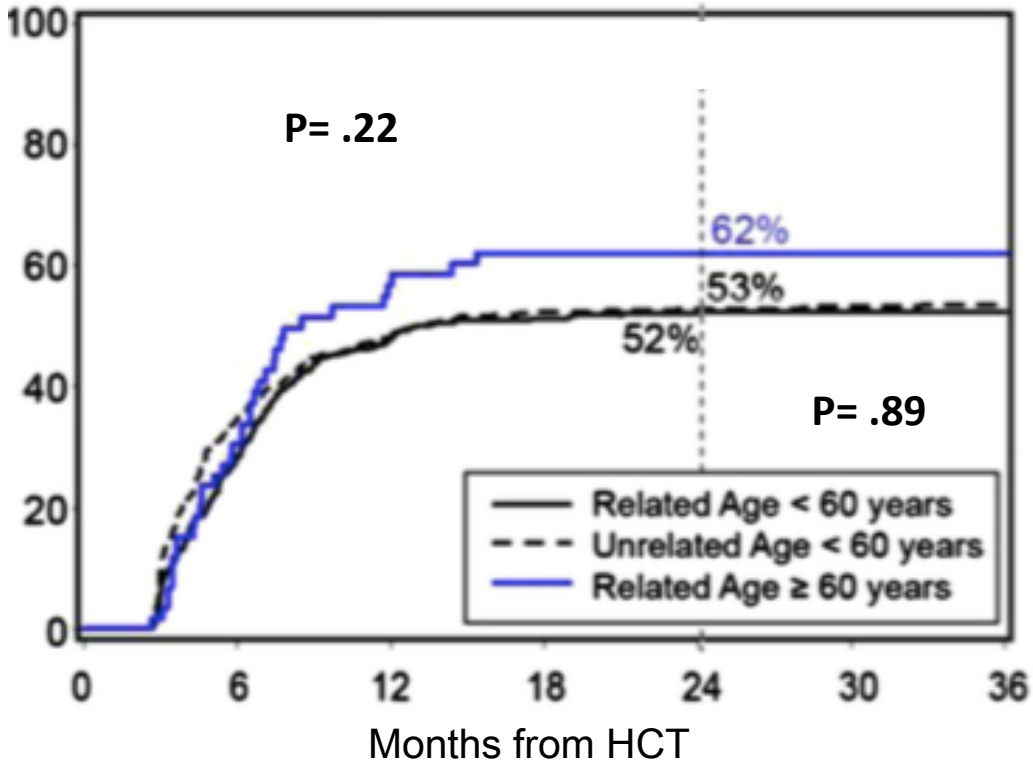
MAC Patients

Grade 2-4 Acute GvHD



Grade 3-4 = NS

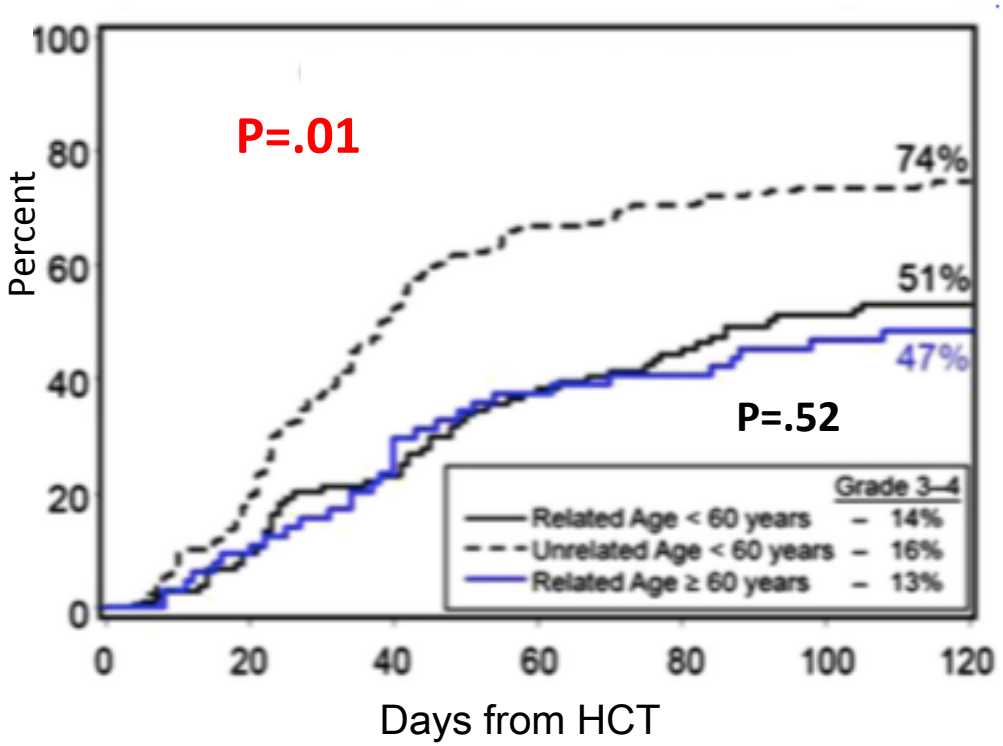
Chronic GvHD



GRAFT versus HOST DISEASE

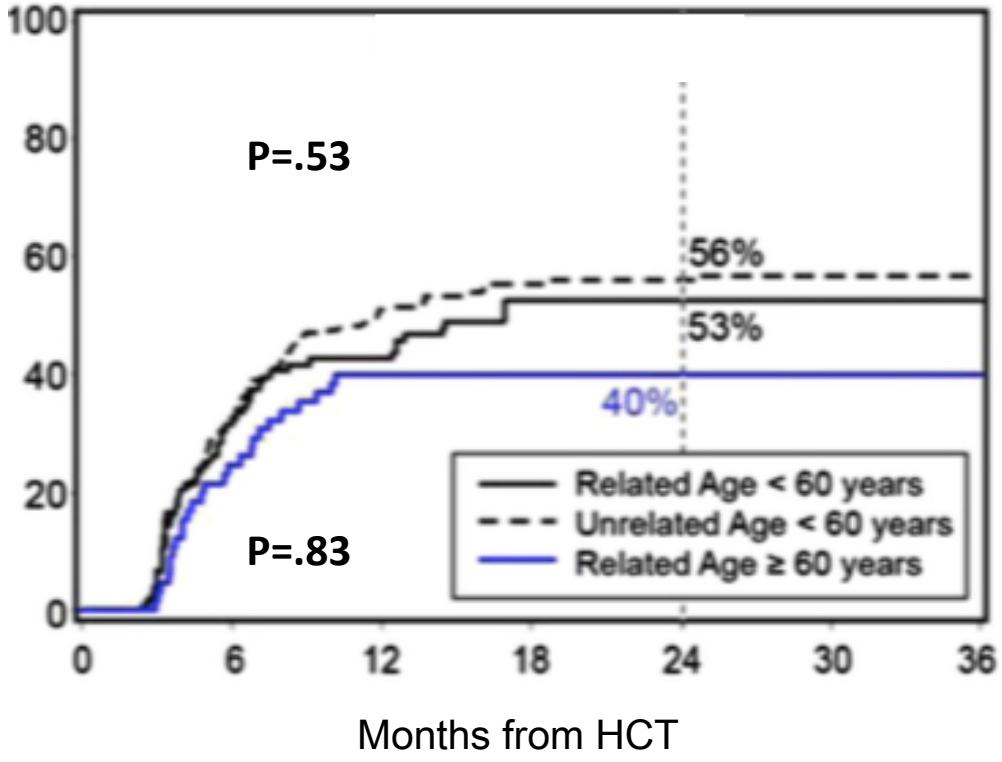
RIC Patients

Grade 2-4 Acute GvHD



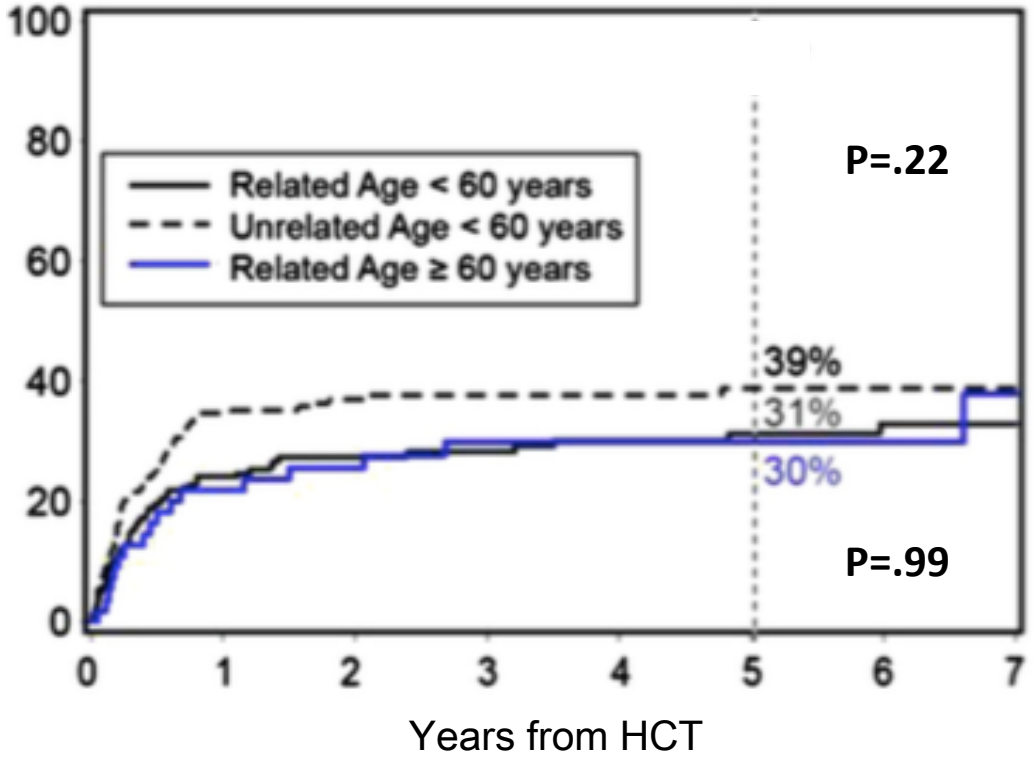
Grade 3-4 = NS

Chronic GvHD

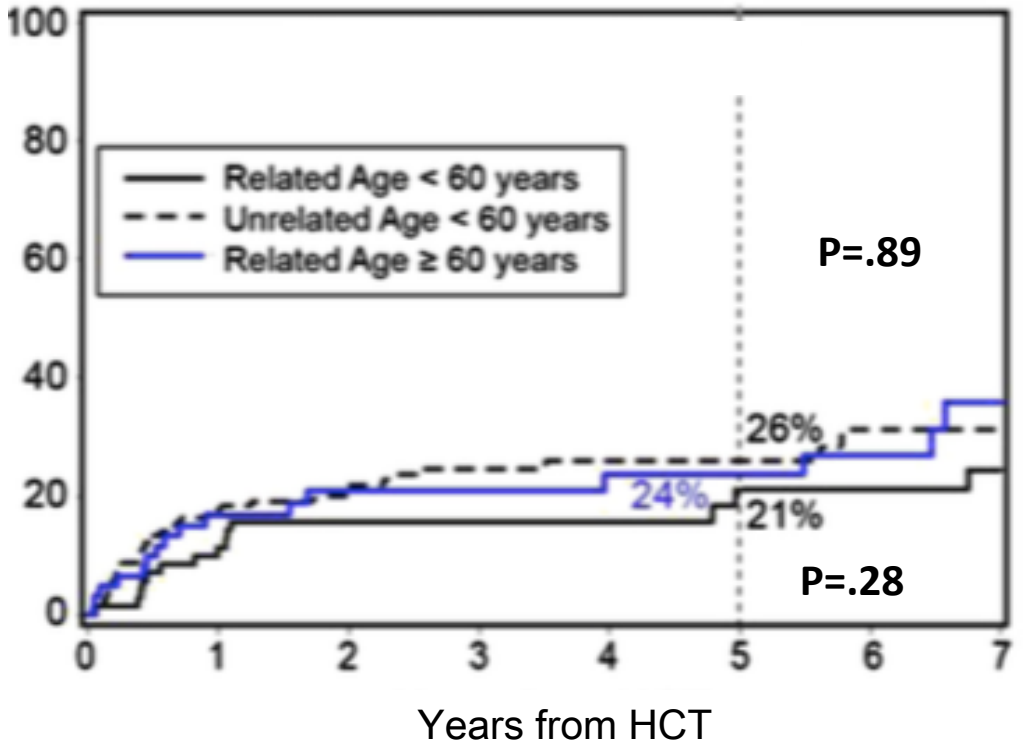


NON-RELAPSE MORTALITY

MAC Patients



RIC Patients



CONCLUSION

- Advanced donor age does not appear to place the recipient at increased risk of delayed engraftment, prolonged neutropenia, prolonged thrombocytopenia, graft rejection, or the development of malignant clonal disorders arising from donor cells
- The risk of acute GVHD grades II to IV is significantly lower with older sibling donors compared with younger HLA-matched unrelated donors
- This study confirms the impact of CD34+ cell dose on engraftment

Grafts from donors >60 years old DO NOT adversely affect outcomes of allogeneic HCT compared with grafts from younger donors

Rezvani AR, … Storb R. BBMT 2015;21:105-112

Who is the better donor for older hematopoietic transplant recipient: an older-aged sibling or a young, matched unrelated volunteer?

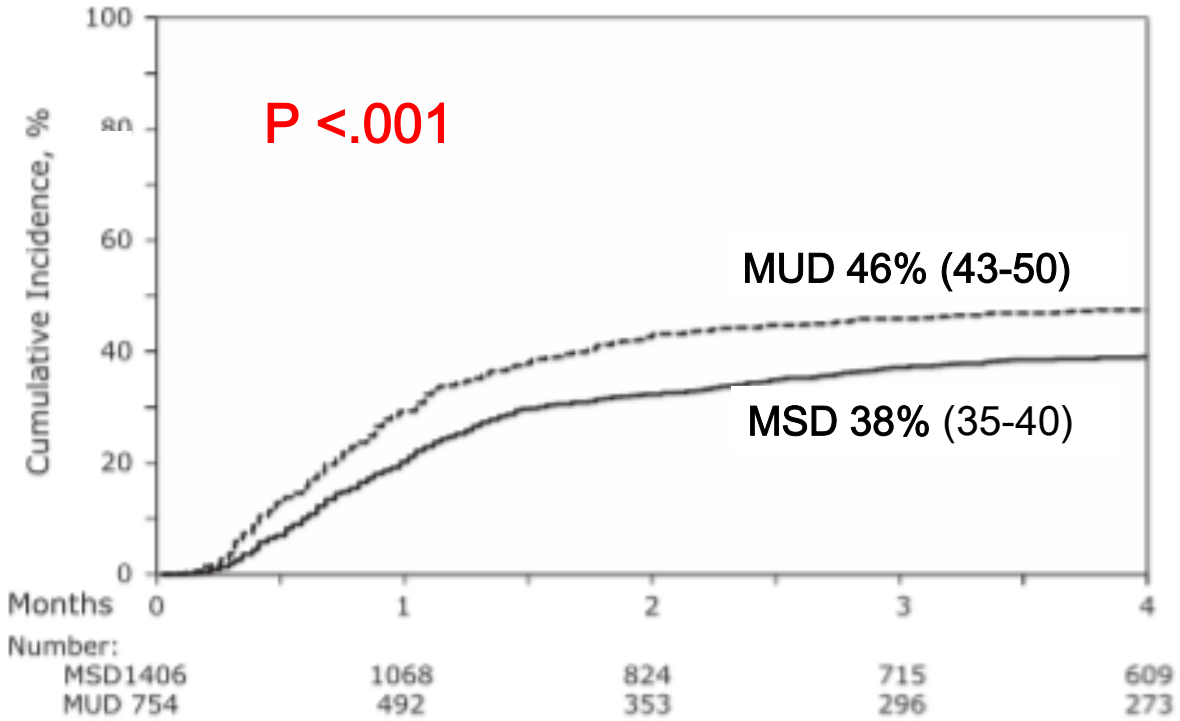
- Retrospective, multicenter study (CIBMTR, 1995-2005)
- Study population: 2172 patients (Leukemia, MDS, Lymphoma)

	Matched sibling Age ≥ 50 yrs	Matched unrelated (8/8) Age < 50 yrs
No. of patients	1415	757
No. of Tx Centers	176	90

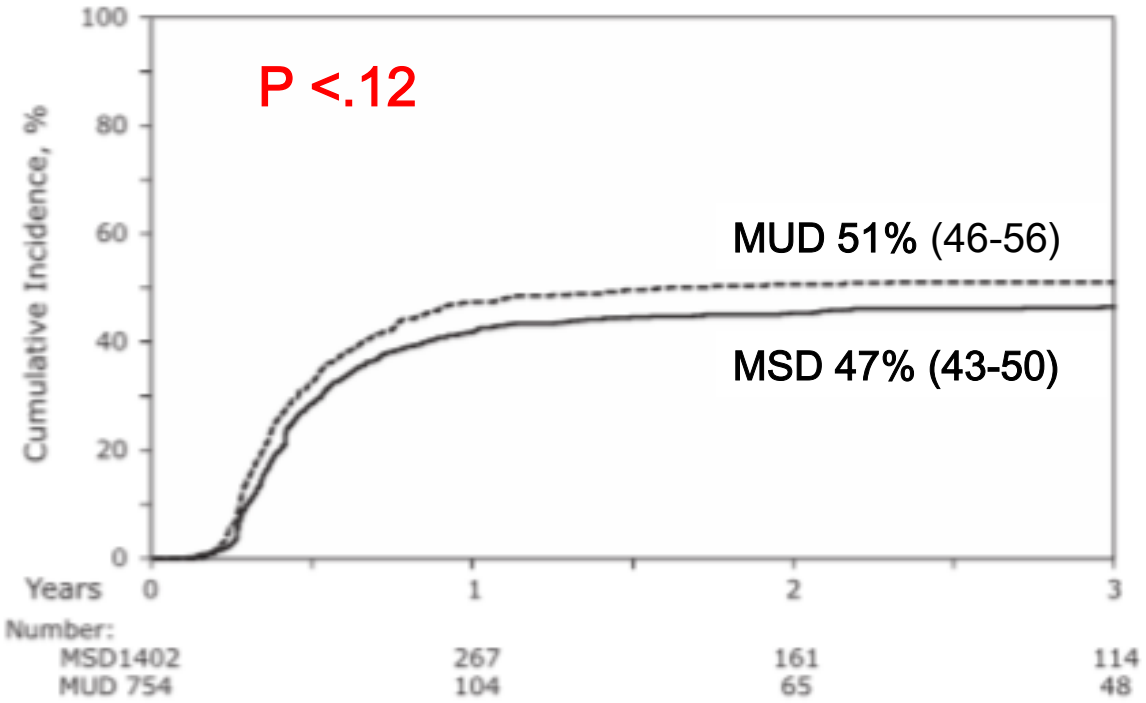
Notably, the 2 groups were significantly differ for many characteristics (PS, disease, in vivo T-cell depletion, GvHD prophylaxis, SC source, sex match, CMV serostatus, donor age, year of Tx)

Alousi AM et al. Blood, 2013 (121):13;2567-73

ACUTE GRAFT versus HOST DISEASE II-IV



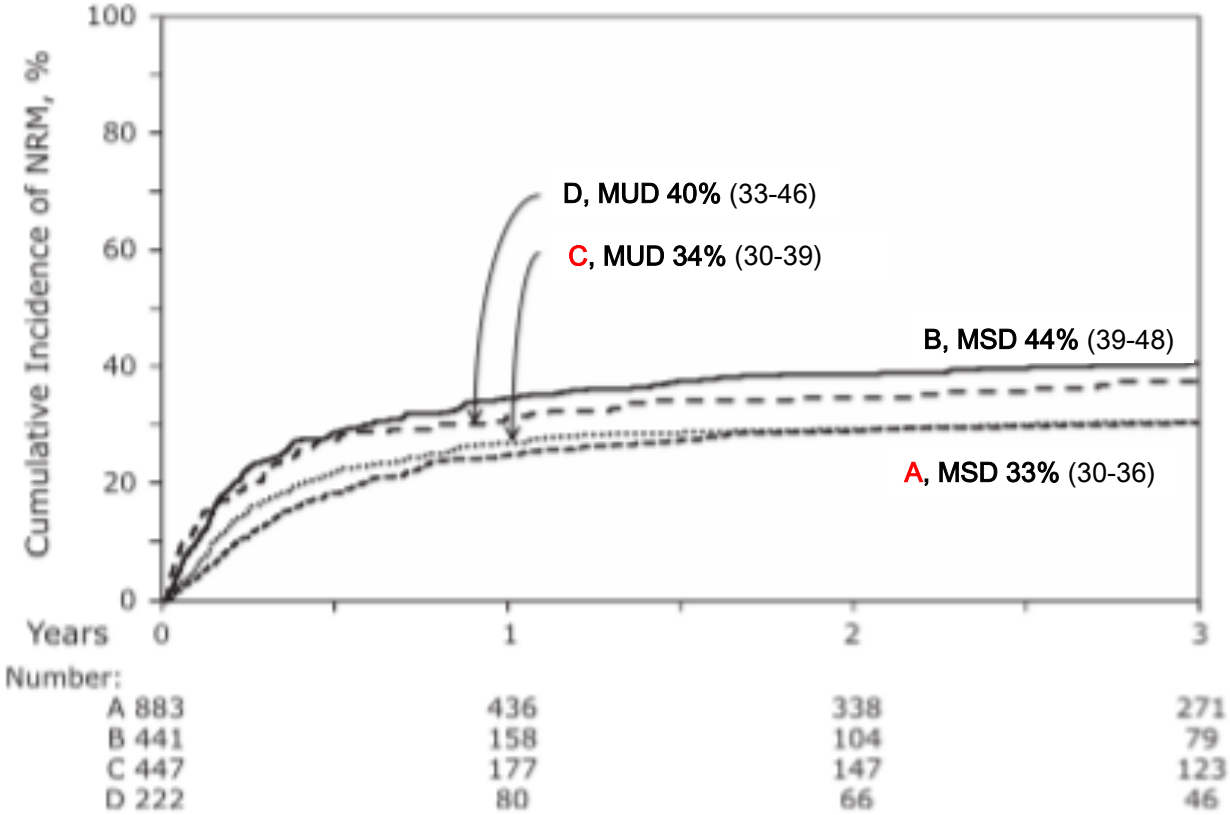
CHRONIC GRAFT versus HOST DISEASE @ 3 years



MULTIVARIATE ANALYSIS FOR ACUTE AND CHRONIC GVHD

Outcome	No. of events/no. evaluable	HR (95% CI)	*P*
Grade 2-4 acute GVHD*			
MSD	560/1406	1.00	
MUD	367/754	1.73 (1.48-2.01)	<.001
Grade 3-4 acute GVHD†			
MSD	306/1406	1.00	
MUD	228/754	1.85 (1.54-2.23)	<.001
Chronic GVHD‡			
MSD	562/1402	1.00	
MUD	361/754	1.48 (1.29-1.70)	<.001

NON –RELAPSE MORTALITY

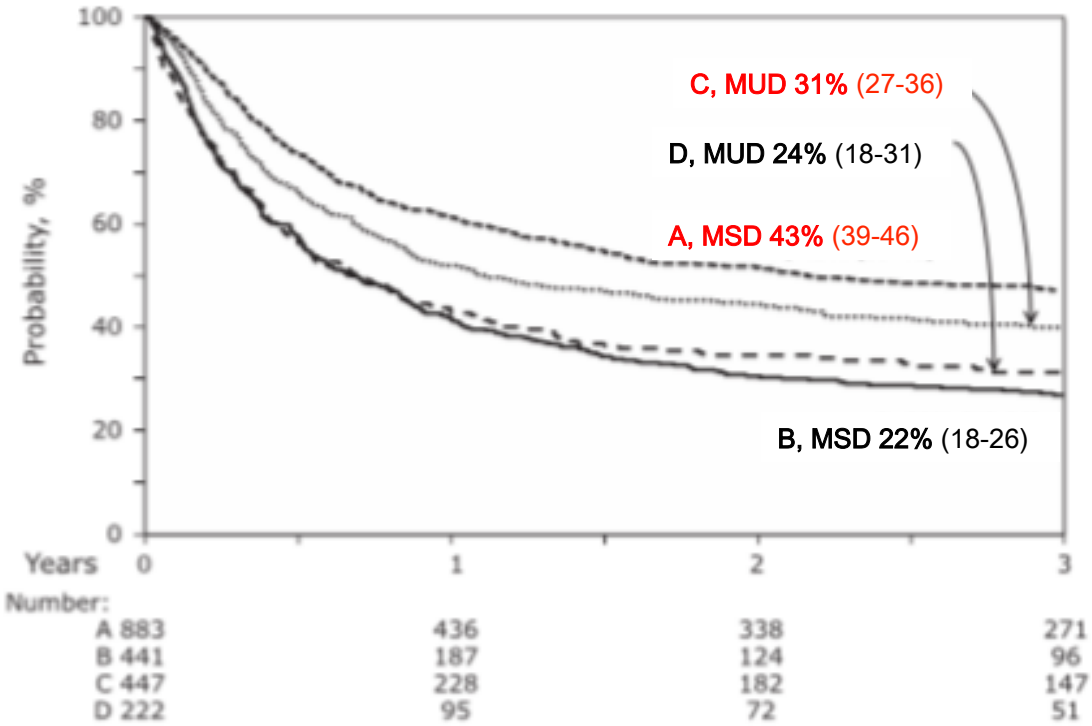


A = recipients of MSD transplants with donors age 50 years or older and performance scores 90 or 100
B = recipients of MSD transplants with donors age 50 years or older and performance scores 80 or lower
C = MUD transplants with donors age younger than 50 years and performance scores 90 or 100
D = MUD transplants with donors age younger than 50 years and performance scores 80 or lower

Multivariate analysis: NRM, RELAPSE, OVERALL MORTALITY, TREATMENT FAILURE

Outcome	No. of events/no. evaluable	HR (95% CI)	*P*
Nonrelapse mortality*			
MSD/PS ≥90	277/883	1.00	
MUD/PS ≥90	151/441	1.42 (1.15-1.74)	.001
MSD/PS ≤80	199/477	1.00	
MUD/PS ≤80	84/222	0.96 (0.74-1.24)	.76
Relapse†			
MSD/PS ≥90	252/883	1.00	
MUD/PS ≥90	167/441	1.57 (1.29-1.91)	<.001
MSD/PS ≤80	179/477	1.00	
MUD/PS ≤80	81/222	0.86 (0.66-1.12)	.25
Overall mortality‡§			
MSD/PS ≥90	479/883	1.00	
MUD/PS ≥90	293/441	1.66 (1.45-1.91)	<.001
MSD/PS ≤80	358/477	1.00	
MUD/PS ≤80	160/222	0.90 (0.75-1.09)	.29
Treatment failure‖			
MSD/PS ≥90	529/883	1.00	
MUD/PS ≥90	318/441	1.63 (1.43-1.87)	<.001
MSD/PS ≤80	378/477	1.00	
MUD/PS ≤80	165/222	0.88 (0.73-1.06)	.18

OVERALL SURVIVAL ADJUSTED FOR CONDITIONING REGIMEN, PATIENT AGE, DISEASE, AND DISEASE STATUS



A vs C: P= <.001
B vs D: P= .18

A = MSD transplants with donors age 50 years or older and performance scores 90 or 100
B = MSD transplants with donors age 50 years or older and performance scores 80 or lower
C = MUD transplants with donors age younger than 50 years and performance scores 90 or 100
D = MUD transplants with donors age younger than 50 years and performance scores of 80 or lower

Subset analysis: PATIENT AGE, DONOR AGE, DONOR SOURCE

	Grade 2-4 acute GVHD		Grade 3-4 acute GVHD		Chronic GVHD		Overall mortality	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Patients 50-59 y								
MUD <50 y (n = 550)	1.00		1.00		1.00		1.00	
MSD ≥50 y (n = 1013)	0.62 (0.53-0.73)	<.001	0.50 (0.41-0.62)	<.001	0.66 (0.56-0.77)	<.001	0.92 (0.81-1.05)	.22
Patients ≥60 y								
MUD <50 y (n = 204)	1.00		1.00		1.00		1.00	
MSD <67 y (n = 299)	0.61 (0.46-0.81)	<.001	0.69 (0.47-0.99)	.043	0.73 (0.56-0.96)	.025	0.78 (0.63-0.97)	.028
MSD ≥67 y (n = 94)	0.67 (0.45-0.99)	<.04	0.62 (0.36-1.06)	.08	0.61 (0.39-0.93)	.023	1.23 (0.92-1.63)	.16

CONCLUSION of THE STUDY = FINAL CONSIDERATIONS

Patients ≥ 50 yrs with PS ≥ 90	Sibling donor ≤ a 67 yrs (if available) better than younger age MUD
Patients with PS ≤ 80 and/or donor ≥ 60 yrs	Matched sibling donor (if available) favored
Patients with high risk disease (urgent transplant)	Easy access to matched sibling donor
Older matched sibling donors	More likely to have comorbidities that may preclude donation
Graft type (BM vs PBSC)	No difference in terms of DFS and OS
$CD34^+$ cell dose	To optimize mobilizing SC collection from older donors

…….. a case-by-case basis decision……..