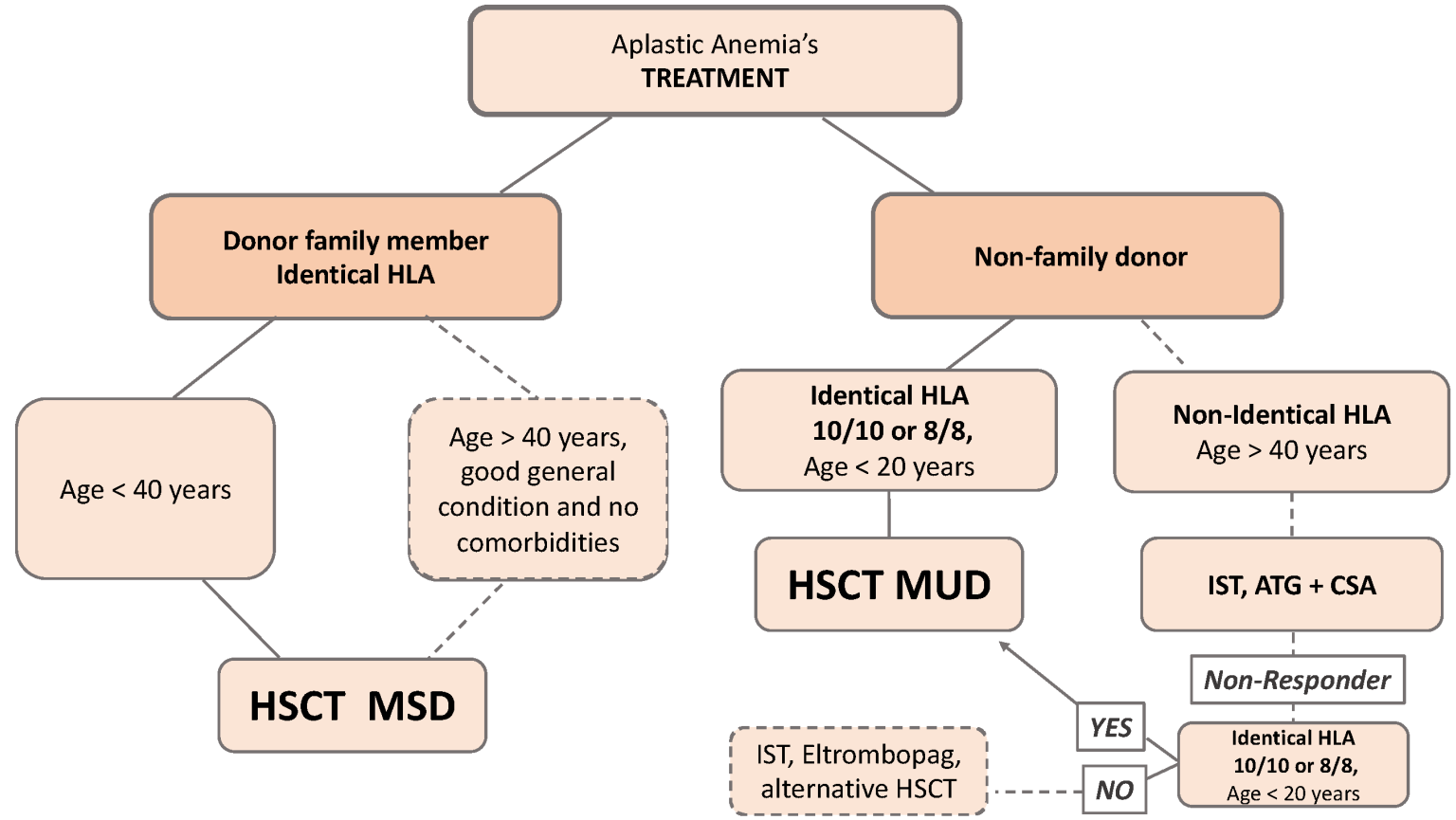
# Role of Alternative donors in aplastic anemia

Sayeh Parkhideh

*Flow chart for Aplastic anemia's treatment*



- The overall response rate at 3 months in patients receiving
- horse ATG (hATG) and CsA is between 60% and 80%.
- In responders, relapse has been reported in 35% of patients by 5 years, and evolution to MDS can occur in up to 20% of patients, highlighting the need for more definitive therapy.

Evaluated biomarkers potentially predictive of better response to IST are as follows

- baseline absolute lymphocyte count ≥1 × 109
- absolute reticulocyte count ≥25 × 10 9 /L

**Poor response** to IST might be expected with an undetectable PNH clone and a shorter telomere length

detection of adverse genetic mutations: ASXL1, DNMT3ARUNX1, TP53

TPO plasma levels of >1,796.7 pg/ml

# improved outcomes of alloHCT from MUDs

- **better high-resolution donor typing**, improved **supportive care**, and
- **the use of Flu and rATG or alemtuzumab** in conditioning protocols
- **with the avoidance of higher doses of TBI** and **PB as a** source of
- hematopoietic cell

- **Should HCT Remain a Priority for Adults With SAA Who Lack a MRD?**

CLINICAL TRIALS CORNER | OCTOBER 24, 2023

# Two National Clinical Trials Poised to Expand the Role of Bone Marrow Transplant in Newly Diagnosed Severe Aplastic Anemia

Lori Muffly, MD, MS

*The Hematologist* (2023) 20 (6)

## STUDY TITLE: A Phase III Randomized Trial Comparing Unrelated Donor Bone Marrow Transplantation With Immune Suppressive Therapy for Newly Diagnosed Pediatric and Young Adult Patients With Severe Aplastic Anemia (TransIT, BMT CTN 2202)

## STUDY TITLE: CUREAA: Clinical Trial of Upfront Haploidentical or Unrelated Donor BMT to REstore Normal Hematopoiesis in Aplastic Anemia

Haploidentical

# Upfront Alternative Donor Transplant versus Immunosuppressive Therapy in Patients with Severe Aplastic Anemia Who Lack a Fully HLA-Matched Related Donor: Systematic Review and Meta-Analysis of Retrospective Studies, on Behalf of the Severe Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation

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Matched unrelated donor transplantation

A B S T R A C T

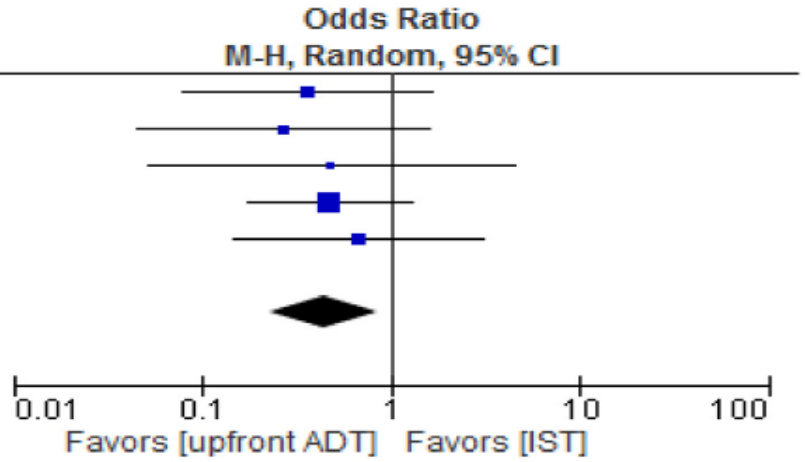
Idiopathic aplastic anemia is a rare and life-threatening disorder, and hematopoietic stem cell transplantation (HSCT) from a matched sibling donor (MSD) is the standard treatment strategy for young patients. Alternative donor transplantation (ADT) from a matched unrelated donor or an HLA haploidentical donor is not commonly used in the frontline setting. This systematic review/meta-analysis was conducted to compare ADT as an upfront, rather than delayed, treatment strategy in the absence of an MSD to immunosuppressive therapy (IST) in severe aplastic anemia (SAA). We searched PubMed/MEDLINE and Embase (1998 to 2019) for studies that compared the outcomes of ADT with IST as upfront therapy in patients with SAA. We included studies with 5 patients or more in each arm. Studies that included patients with inherited forms of bone marrow failure syndromes were excluded. The primary outcome was the 5-year overall survival (OS) rate. Five studies met the inclusion criteria and were included in this meta-analysis. The pooled 5-year odds ratio (OR) for OS was statistically significant at 0.44 (95% confidence interval [CI], 0.23 to 0.85) in favor of upfront ADT. In addition, survival was compared between upfront ADT versus salvage ADT in 6 studies. The pooled 5-year OR for OS was statistically significant at 0.31 (95% CI, 0.15 to 0.64) in favor of upfront ADT. Although this analysis has some limitations, including the retrospective nature of the included studies, the lack of ethnic diversity, the predominantly pediatric population, and the relatively suboptimal IST regimen used in some of the studies, it indicates that upfront ADT is a potential alternative treatment option in young and pediatric SAA patients who lack an HLA identical sibling donor, particularly when optimal IST is not available.

this meta-analysis suggests that upfront ADT could be a potential option in pediatric and young adult patients with SAA who lack an HLA-identical sibling donor, particularly when optimal IST is not availabl

a

| Study or Subgroup | Upfront ADT Events | Upfront ADT Total | IST Events | IST Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Cheng 2018 | 3 | 28 | 6 | 24 | 18.4% | 0.36 [0.08, 1.63] |
| Choi 2017 | 2 | 23 | 5 | 19 | 13.4% | 0.27 [0.05, 1.57] |
| Dufour 2015 | 1 | 29 | 4 | 58 | 8.4% | 0.48 [0.05, 4.52] |
| Xu ZL 2019 | 10 | 76 | 9 | 37 | 41.7% | 0.47 [0.17, 1.29] |
| Yang 2019 | 3 | 20 | 6 | 29 | 18.2% | 0.68 [0.15, 3.10] |
| **Total (95% CI)** | | **176** | | **167** | **100.0%** | **0.44 [0.23, 0.85]** |
| Total events | 19 | | 30 | | | |

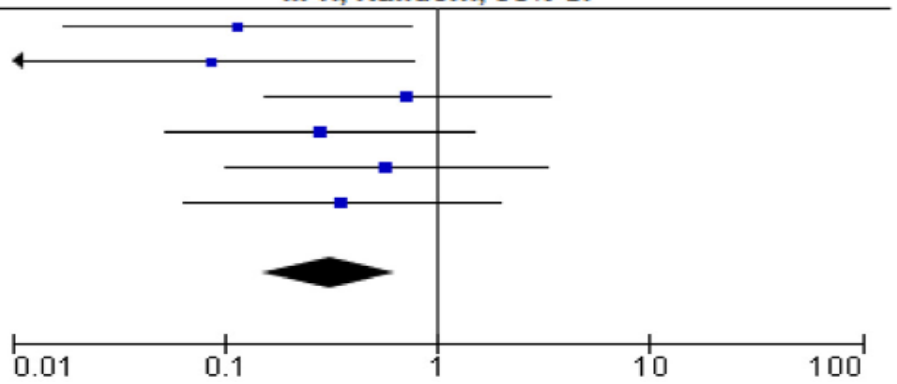
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 4 (P = 0.95); I² = 0%
Test for overall effect: Z = 2.45 (P = 0.01)




b

| Study or Subgroup | upfront ADT Events | upfront ADT Total | salvage ADT Events | salvage ADT Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Choi 2017 | 2 | 23 | 5 | 11 | 14.7% | 0.11 [0.02, 0.74] |
| Dufour 2015 | 1 | 29 | 7 | 24 | 10.9% | 0.09 [0.01, 0.77] |
| Xu LP 2017 | 3 | 23 | 5 | 29 | 21.5% | 0.72 [0.15, 3.39] |
| Xu LP 2018 | 5 | 41 | 3 | 9 | 18.5% | 0.28 [0.05, 1.48] |
| Yamei 2017 | 5 | 62 | 2 | 15 | 16.9% | 0.57 [0.10, 3.27] |
| Yang 2019 | 3 | 20 | 4 | 12 | 17.5% | 0.35 [0.06, 1.96] |
| **Total (95% CI)** | | **198** | | **100** | **100.0%** | **0.31 [0.15, 0.64]** |
| Total events | 19 | | 26 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 4.07, df = 5 (P = 0.54); I² = 0%



Transplantation and Cellular Therapy

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ASTCT American Society for Transplantation and Cellular Therapy

Guideline

# Allogeneic Hematopoietic Cell Transplantation for the Treatment of Severe Aplastic Anemia: Evidence-Based Guidelines From the American Society for Transplantation and Cellular Therapy

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The panel utilized **the Grading of Recommendation**, Assessment, Development and Evaluation (GRADE) approach

- **GRADE methodology**
- mini systematic reviews and meta-analyses were conducted, including studies published through December 2023 to address guideline questions.
- All questions were sent to panel members to develop recommendations based on evidence synthesized. More than 80% consensus was required before accepting a recommendation

- **The Recommendations** are labelled as “**strong**’’
- or “**conditional/weak’’** according to the GRADE approach.

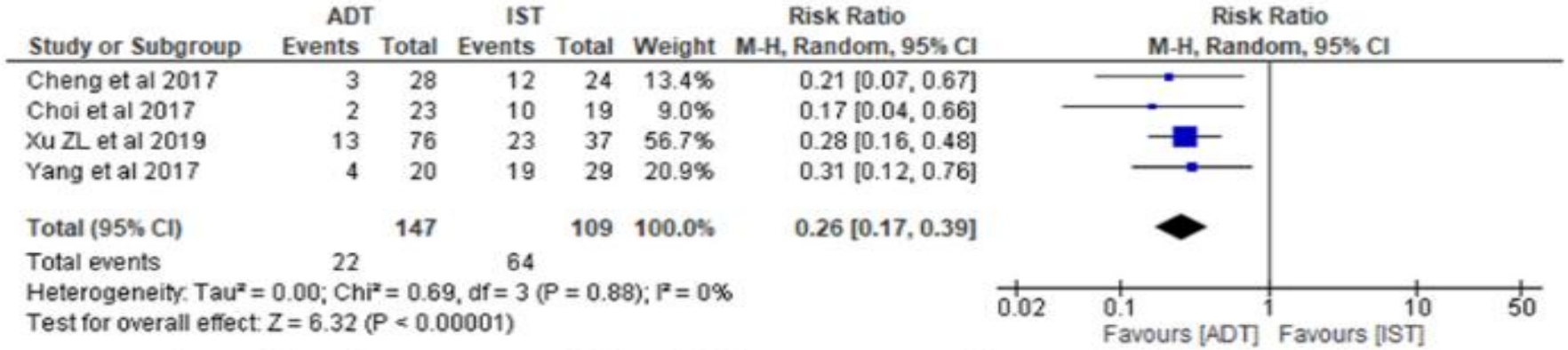
**Table 1**
Summary of Recommendations and Evidence Grading

| Guideline Question and Recommendation | Quality of Evidence | Strength of Recommendation | Level of Agreement |
|---|---|---|---|
| Disease and patient assessment prior to HCT | | | |
| *Question 1: How should patients with suspicion of SAA be assessed prior to HCT?* The panel recommends that all AA patients should undergo testing to confirm the diagnosis and look for underlying causes of BMF. All newly diagnosed AA should be assessed for indications for HCT and initiation of donor search | Good practice statement | Good practice statement | 100% |
| *Question 2: Should an age cutoff of 40 yr be used for adult patients receiving HCT for SAA?* Due to improvement in supportive care and conditioning regimen, our panel suggests that upfront HCT may be considered up to 50 yr of age or beyond for patients with severe cytopenias in centers with expertise in HCT | ⊕⊕⊕◯ Moderate | Conditional | 100% |
| Decision for HCT | | | |
| *Question 3: Should MRD or IST be used for newly diagnosed children and young adults patients with SAA ?* We recommend upfront MRD-HCT for pediatric and AYA patients presenting with severe aplastic anemia as it offers high cure rates with minimal risk of GVHD, rejection or disease transformation | ⊕⊕⊕◯ Moderate | Strong | 100% |
| *Question 4: Should MRD-HCT be prioritized over IST for newly diagnosed adults with SAA ?* Our panel recommends MRD-HCT as a preferred first-line treatment for patients up to 50 yr of age or beyond | ⊕⊕⊕◯ Moderate | Strong | 100% |
| Donor selection | | | |
| *Question 5: Should HCT be prioritized over IST for children and young adults who lack a MRD?* The panel suggests upfront HCT (either MUD or Haplo-HCT) for pediatric patients lacking a MRD. For patients failing the first course of IST, the panel recommends HCT (either MUD or Haplo-HCT) over the second course of IST | ⊕◯◯◯ Very Low | Conditional | 85.7% |
| *Question 6: Should HCT remain a priority for adults with SAA who lack a a MRD?* The panel suggests the use of either MUD or haplo-HCT in preference to IST for patients with SAA lacking a MRD | ⊕⊕◯◯ Low | Conditional | 88% |
| *Question 7: Should MUD-HCT be prioritized over Haplo-HCT for patients lacking a MRD?* The panel suggests either MUD or haplo-HCT for patients lacking a MRD | ⊕⊕◯◯ Low | Conditional | 86% |
| HCT procedures | | | |
| *Question 8: Should rabbit ATG or horse ATG be used in con* | | | 93% |

# Question 6: Should HCT Remain a Priority for Adults With SAA Who Lack a MRD?

- Recommendation
- **The panel suggests either MUD or haplo-HCT for patients without a MRD** (Strength of recommendation, **Conditional**; Certainty of evidence, low ⨁⨁


**1a: Overall Survival for adult patients undergoing ADT vs IST**




**b: Failure free Survival for adult patients undergoing ADT vs IST**

**Figure 1.** (A) Overall Survival for adult patients undergoing ADT vs IST. (B) Failure free Survival for adult patients undergoing ADT vs IST.

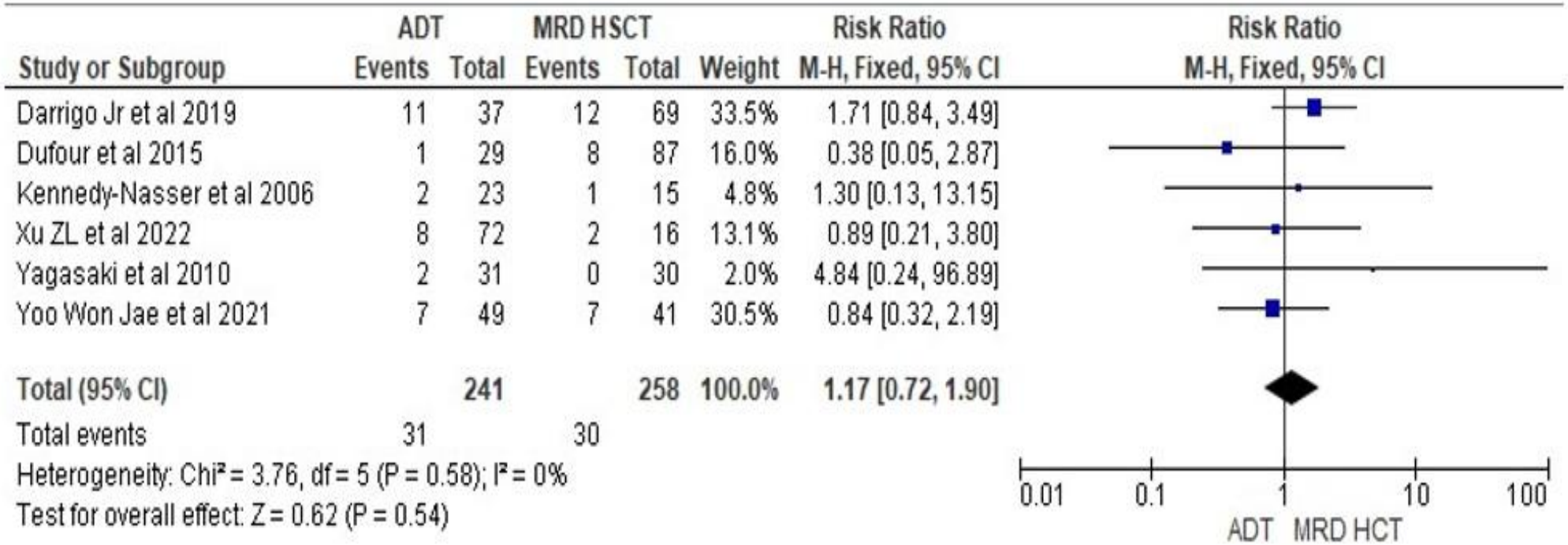



**Figure 4A: Overall Survival between ADT and MRD-HCT**

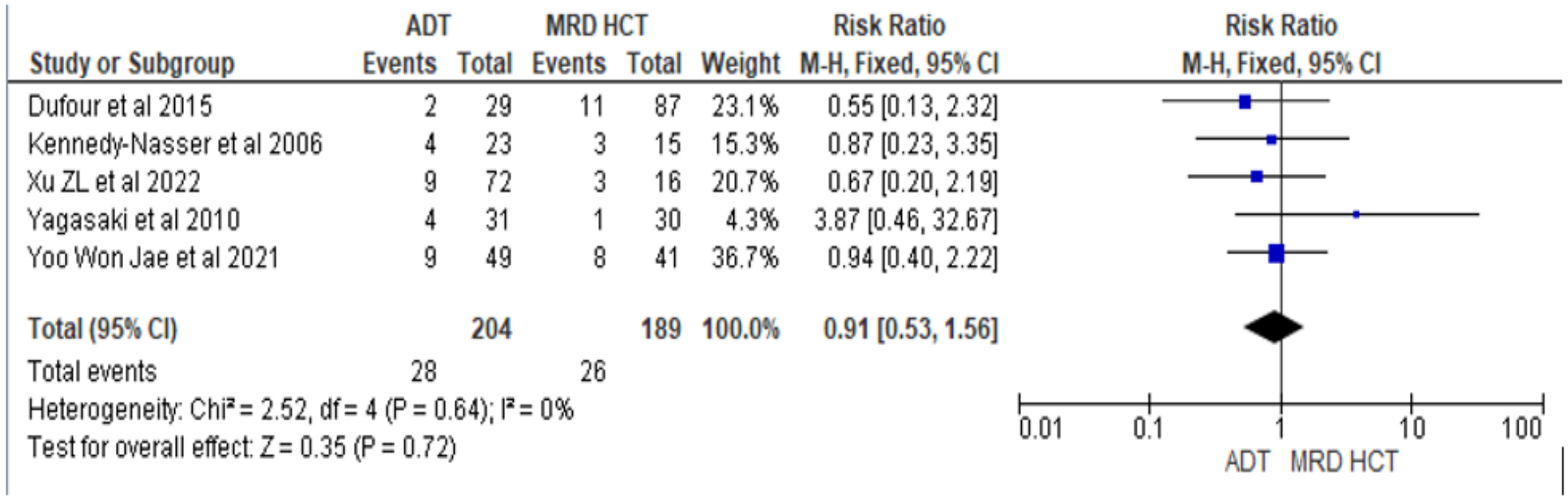



**Figure 4B: Failure free survival between ADT and MRD-HCT**

# Question 7: Should MUD-HCT Be Prioritized Over Haplo-HCT for Patients Lacking a MRD?

- The panel suggests either a MUD or haplo-HCTfor patients lacking a MRD (Strength of recommendation, conditional; Certainty of evidence, low ⊕⊕ ) with insufficient evidence for prioritizatio

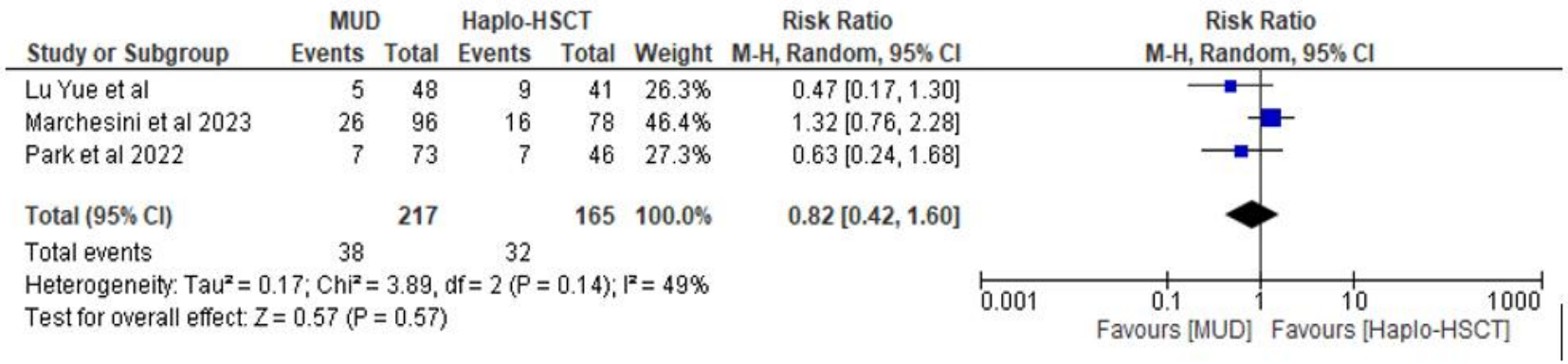



**Figure 5a: Overall Survival MUD-HCT vs Haplo-HCT**

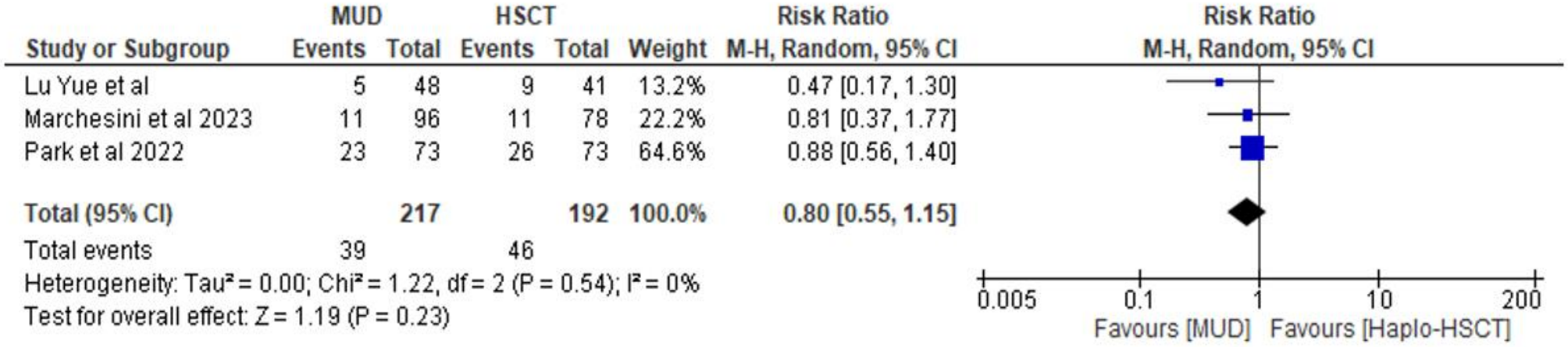



**Figure 5b: Failure Free Survival MUD-HCT vs Haplo-HCT**

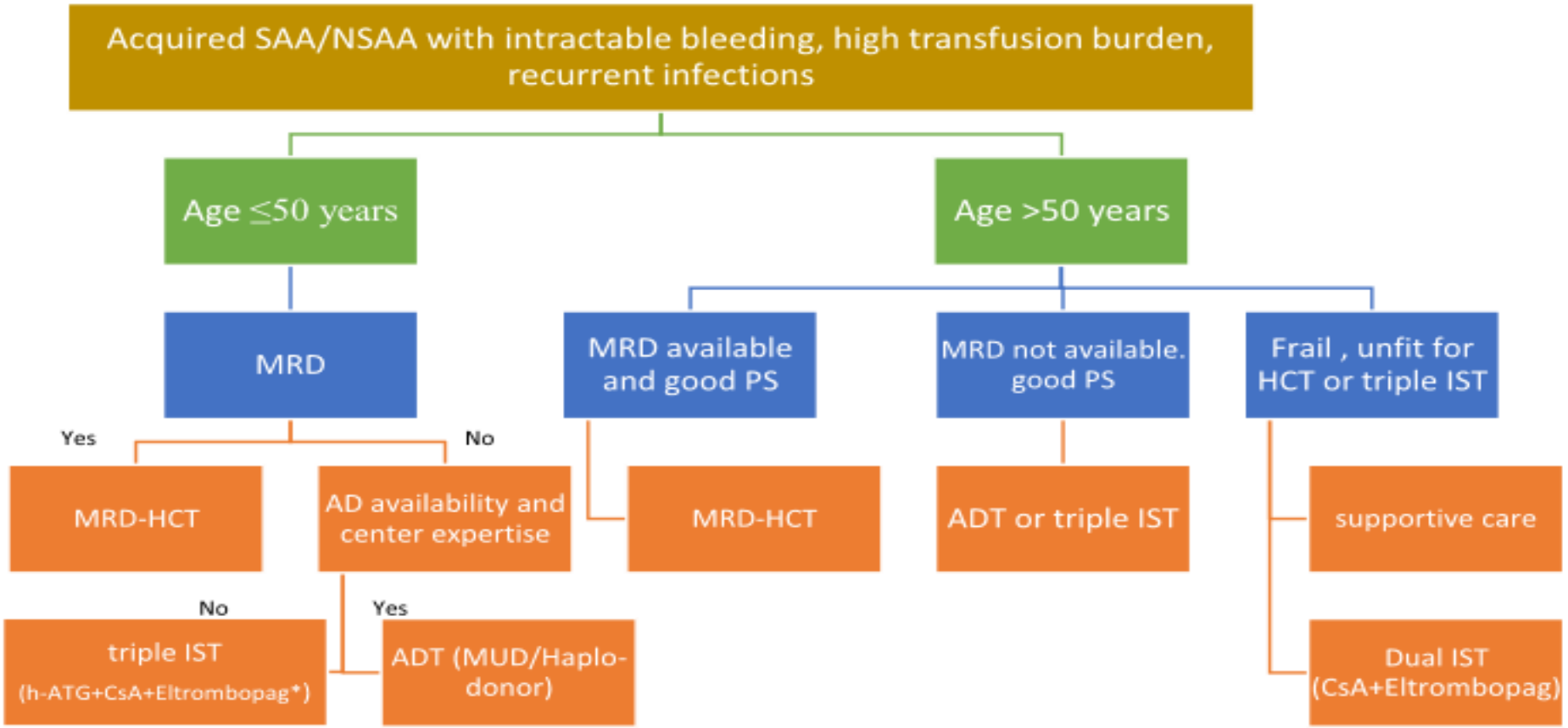



**Figure 2.** Treatment Algorithm of SAA patients. SAA severe aplastic anemia, NSAA non-severe aplastic anemia, MRD (matched related donor), MUD (matched unrelated donor) IST (immunosuppressive treatment), Haplo (Haploidentical), PS performance status, HCT hematopoietic cell transplant, AD alternate donors, CSA ciclosporine, h-ATG horse anti-thymocyte globulin. *Currently there is lack of clear evidence indicating benefit to give eltrombopag in children less than 18 yr of age.

Table 4
Preferred Conditioning Regimens in Acquired Aplastic Anemia

| Donor Type | Conditioning Regimen |
|---|---|
| Matched related donor | Age < 30 yr: CY200 mg/kg + r-ATG [20,88,89] or CY200 mg/kg + Alemtuzumab [75]<br>Age >30 yr: FLU 30 mg/m2 × 4-5 d, CY 300 mg/m2 × 4 d and r-ATG (FCA regimen) [20]<br>High risk of Graft failure: Flu 120-150 mg/m$^2$ + CY 120 mg/kg + r-ATG [15] |
| Matched unrelated donor | Adults:<br>1. FCA-TBI: fludarabine 30 mg/m$^2$ x 4, cyclophosphamide 300 mg/m$^2$ x 4 and ATG 3.75 mg/kg x 2, TBI 2 Gy [1]<br>2. FCC: fludarabine 30 mg/m$^2$ x 4, cyclophosphamide 300 mg/m$^2$ x 4, alemtuzumab 0.2 mg/kg x 5 d (total dose 40-100mg) [76]<br>3. For 9/10 MMUD: FCC plus 2G TBI [1]<br>4. Alternative for 8/8 or 7/8—BMT CTN 0301: fludarabine 30 mg/m$^2$ x 4, cyclophosphamide 50mg/kg x 1 (older patients) or x 2 (pediatric/young adult patients), rATG 3 mg/kg x 3, TBI 2 Gy [90]<br>Pediatric<br>5. Flu 30mg/m$^2$ x 5 d, CY 60 mg/kg x 2 d with r-ATG (5-20 mg/kg) or alemtuzumab 0.3 mg/kg for 3 d and CSA± MTX for GVHD prophylaxis [91]<br>6. 8/8 or 7/8—BMT CTN 0301: fludarabine 30 mg/m$^2$ x 4, cyclophosphamide 50mg/kg x 2, rATG 3 mg/kg x 3, TBI 2 Gy [90] |
| Haplo-HCT | PTCy based:<br>r-ATG 4.5 mg/kg total dose, FLU 30 mg/m2 × 4-5 d, CY 14.5 mg/kg x 2 d and TBI 2-4 Gy (D-1) with PTCy 50 mg /kg x 2 d [92,93] |
| Cord blood | 1. FLU 30 mg/m2 × 4, CY 30 mg/kg x 4, ATG 2.5 mg/kg x 2 and TBI 2 Gy The French protocol (called APCORD) [94]<br>2. FLU 40 mg/m$^2$ per day (d -6 to d -2),CY 30 mg/kg per day (d -5 to d -2), and TBI or total marrow irradiation [95] |
| Syngeneic HCT | Although there is paucity of data, studies recommend use of Cy-ATG conditioning and PB as stem cell source to avoid graft failure [96]. |

# TAKE HOME MASSAGE

long-term risk for disease relapse and secondary MDS/AML after IST.

If a donor can be identified early and patients are treated in centers with expertise in ADT, it is suggested to proceed with upfront MUD or Haplo-HCT