Minimal residual disease prior to allogeneic hematopoietic cell transplantation in acute myeloid leukemia: a meta-analysis

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SUPPLEMENTAL MATERIALS

Supplemental Table 1: Search strategies for PubMed and EMBASE, with additional restrictions on year of publication starting January 1st, 2005 and English-language publications. In EMBASE, only published articles were included.

PubMed strategy	EMBASE strategy
(“acute myeloid leukemia” OR “acute myelogenous leukemia” OR “acute myeloid leukaemia” OR “acute myelogenous leukaemia” OR "acute myeloblastic leukemia" OR "actue myeloblastic leukaemia" OR AML OR "leukemia, myeloid, acute"[MeSH]) **AND** (transplant OR transplantation OR transplanted OR transplants OR transplantations OR HCT OR HSCT OR allogeneic OR BMT OR “stem cell transplantation”[MeSH]) **AND** (“residual disease” OR MRD OR "residual leukemia" OR "stringent complete remission" OR "stringent CR" OR “neoplasm, residual”[MeSH])	('acute myeloblastic leukemia'/exp OR "acute myeloid leukemia" OR "acute myeloid leukaemia" OR "acute myelogenous leukemia" OR "acute myelogenous leukaemia" OR "acute myeloblastic leukemia" OR "acute myeloblastic leukaemia" OR AML) **AND** ('minimal residual disease'/exp OR "residual cancer" OR "residual disease" OR "residual leukemia" OR "residual leukaemia" OR mrd OR “stringent complete remission” OR “stringent CR”) **AND** ('stem cell transplantation'/exp OR HSCT OR HCT OR transplant OR transplants OR transplanted OR transplantation OR allogeneic OR BMT)

Supplemental Table 2: Risk of bias assessment tool used to assign risk of bias

Bias Domains	Study Characteristics	Risk of Bias
Prognostic Factor Measurement	**Pre-HCT measurement of MRD is appropriate** (a) MRD detection method must be clearly described, valid, and reliable. (b) Continuous variables are reported or pre-specified cut points are used. (c) MRD is measured close enough to the start of transplant to capture a true "pre-transplant" state	**High risk**: MRD detection methods not described or likely to be inaccurate based on the following criteria: • MRD measured >60 days before transplant • For MFC, methodology is suspect based on (1) reported sensitivity not consistent with number of cells collected and reagent panels used, (2) details such as cells/tube and antibody panels neither provided nor referenced, (3) center has not had prior publications with referenced protocols if not using their own protocol, or (4) $<10^5$ cells/tube used. • For PCR, methodology is suspect based on (1) >24 hours between specimen collection and RNA extraction, (2) lack of negative and standard controls, and (3) failure to perform the assay with >1 replicate. **Moderate risk**: cut points between MRD+ and MRD- are chosen based on exploratory analysis without a validation cohort and/or time between measurement and transplant not reported. Further, there is insufficient information to assess bias in MFC or PCR methodology. **Low risk**: MRD measurement is valid, with a pre-specified cut-point between MRD+ and MRD-, and MRD is measured within 60 days of transplant.
Study Confounding	**Important potential confounding factors are described** (a) Confounders are measured across all participants and are reported separately for MRD+ and MRD- patients; key covariates are age, cytogenetics, and conditioning intensity. (b) Inclusion of patients not in CR may bias the MRD+ group toward worse outcomes.	**High risk**: no key covariates are reported for MRD+ and MRD- patients. **Moderate risk**: only some key covariates are reported for MRD+ and MRD- patients. **Low risk**: all key covariates are reported for MRD+ and MRD- patients.
Statistical Analysis and Reporting	**The statistical analysis is appropriate, and all primary outcomes are reported** (a) Statistical methods are described, and there is no selective reporting of results (b) Hazard ratios for outcomes should be accurate	**High risk**: the reported results are likely to be biased related to selective reporting of data (not all outcomes described in methods reported in results). **Moderate risk**: hazard ratios and confidence intervals must be extrapolated from survival curves or point-estimates. **Low risk**: hazard ratios with confidence intervals are reported or obtained from individual patient data.

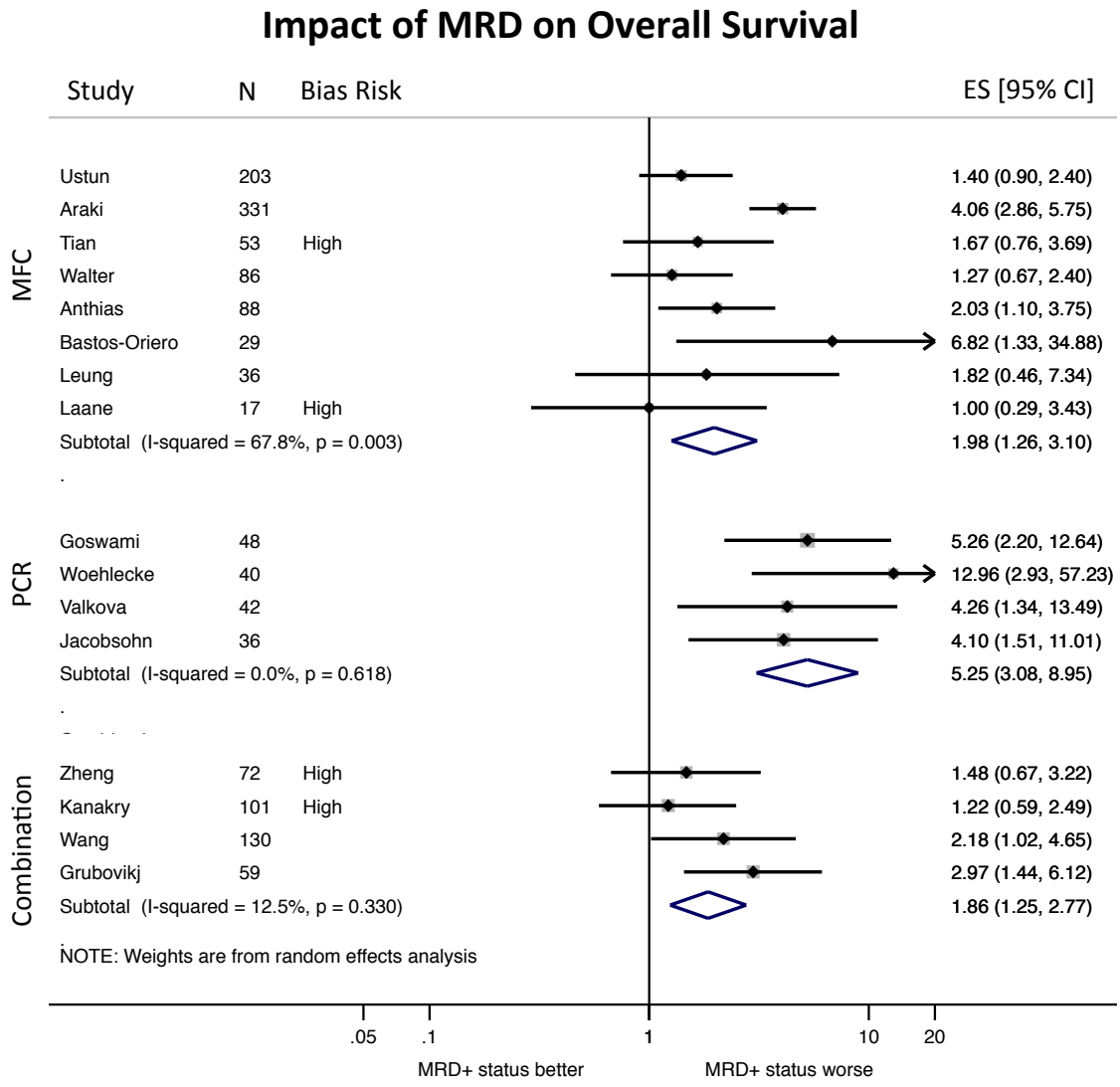
Supplementary Table 3: Details of conditioning regimens, stem cell sources, and GVHD prophylaxis for each study

Study	Conditioning	Stem Cell Source	GVHD Prophylaxis
Bleyzac et al[26]	MA: TBI or Bu-based	43% MRD 14% MURD 43% MMURD	CsA + 7.5 mg/kg rabbit ATG for URD + corticosteroids for CBT
Ustun et al[27]	MA: Cy/TBI [1320 cGy] or Flu/Bu + melphalan or Bu/Cy. *or* RIC: Cy/Flu/TBI [200 cGy] or Flu/Bu ± ATG.	MRD or UCB	CsA + MMF or sirolimus + MMF for UCB or RIC. CsA + MTX for others.
Zheng et al[25]	MA: Bu [12.8 mg/kg] / Cy [120 mg/kg] + HDAC *or* MA: Cy [120 mg/kg] / TBI [1200 cGy] + HDAC	UCB (mostly single unit)	CsA + MMF
Araki et al[24]	MA: various – Bu/Cy ± low-dose TBI, Bu/Flu, Bu/etoposide, Bu/clofarabine, high-dose TBI ± Cy or Flu, high-dose TBI/thiotepa/Flu, treosulfan/Flu ± low-dose TBI, Flu/low-dose TBI + radiolabeled antibody ± Cy	40% MRD 60% unrelated donor	CI + MTX (73%), CI + MMF (11%), Cy ± CI ± MMF (13%), other (3%)
Goswami et al[31]	MA (92%): Cy [120 mg/kg] / TBI or Flu [125 mg/m^2] / Cy / TBI [1200-1360 cGy except 600 cGy for older adults in some cases] *or* RIC: Flu-based [125 mg/m^2]	Mostly MRD, T-cell depleted	CsA
Rossi et al[19]	MA: Cy [120 mg/kg] / TBI [1200 cGy] *or* MA: Bu [9.6 mg/kg] + tepadine [10 mg/kg] + Flu [150 mg/m^2]	54% MRD, 33% MURD, 13% MMRD	CI + MTX + ATG. Cy added for MMRD
Tian et al[28]	MA: Bu [9.6 mg/kg] / Cy [3.6 g/m^2] *or* MA: TBI [750 cGy] / Cy [3.6 g/m^2] *or* MA: Bu or TBI/Cy + rabbit ATG	53% MRD 21% MURD 26% MMRD Some had planned DLI day 26 provided no GVHD	CSA + MMF + MTX
Walter et al[29]	RIC: low-dose TBI ± Flu or clofarabine	44% MRD 66% unrelated donor	CI + MMF ± rapamycin
Woehlecke et al[30]	MA (subset): mostly TBI or Bu-based	30% MRD 46% MURD 24% MMURD	Not listed
Anthias et al[22]	MA: Cy / TBI ± alemtuzumab (for URD) *or* RIC Flu + melphalan + alemtuzumab	34% MRD 57% unrelated donor 9% UCB	Not listed
Bastos-Oriero et al[33]	Not listed (86% MA)	46% MRD 32% MURD 15% UCB 7% MMRD	Not listed
Kanakry et al[21]	MA: Bu [targeted] /Cy [100 mg/kg] or Bu [targeted] / Flu [160 mg/m^2]	57% MRD 43% MURD	Post-transplant Cy [50 mg/kg days +3 and +4]

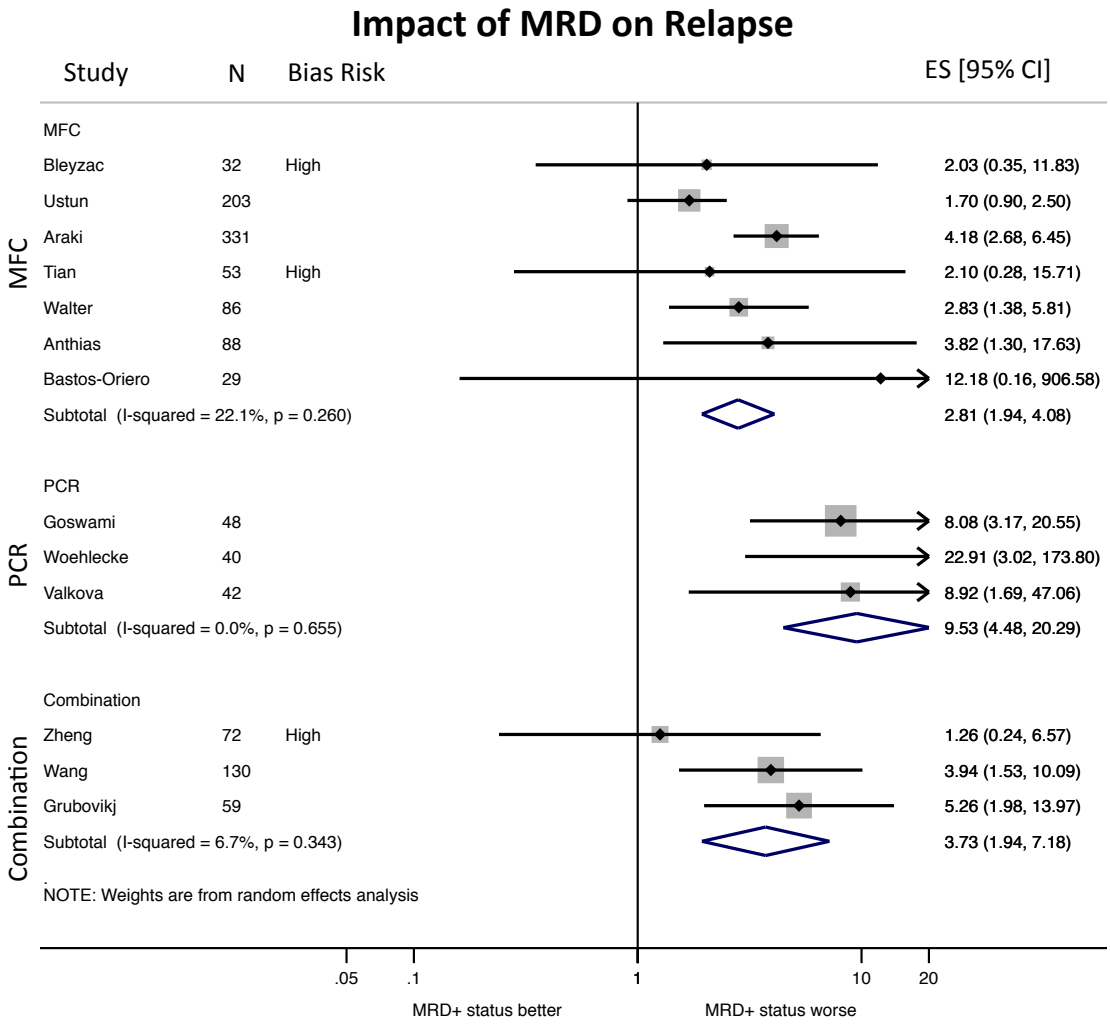
Wang et al[34]	MA: cytarabine [8 g/m^2] + Bu [9.6 or 12 mg/kg] + Cy [3.6 g/m^2] + semustine [250 mg/m^2] ± ATG	100% MMRD	CSA + MMF + MTX
Grubovikj et al[35]	88% MA 46% TBI-based	57.6% related 78% matched	Not listed
Leung et al[36]	MA: TBI/Cy (for matched) *or* MA: TBI-based or Flu + melphalan-based regimens (for haploidentical)	Not listed T-cell depletion used for haploidentical	CsA + MTX or MMF
Valkova et al[32]	MA: TBI or Bu-based *or* RIC: Flu + Bu or melphalan or TBI [200 cGy]	38% MRD 38% MURD 24% MMURD	CI ± MMF
Candoni et al[17]	RIC: Flu/Bu, Cy/thiotepa, treosulfan/Flu	56% MRD 38% URD 6% UCB	Not listed
Jacobsohn et al[18]	MA: TBI [1200 cGy] / Cy [120 mg/kg] + etoposide [1 g/m^2] *or* MA: Bu [12.8 mg/kg] / Cy [240 mg/kg] *or* RIC: Flu [180 mg/m^2] / Bu [targeted] + rabbit ATG	36% MRD 17% MURD 47% UCB	Not listed
Laane et al[37]	Not listed (100% MA)	Not listed	Not listed

Abbreviations: ATG, anti-thymocyte globulin; Bu, busulfan; CBT, cord blood transplant; CI, calcineurin inhibitor; CsA, cyclosporine A; Cy, cyclophosphamide; Flu, fludarabine; GVHD, graft-versus-host disease; HDAC, high-dose cytarabine; MA, myeloablative; MMF, micophenolate mofetil; MMRD, mismatched related donor; MMURD, mismatched unrelated donor; MRD, matched related donor; MTX, methotrexate; MURD, matched unrelated donor; RIC, reduced intensity conditioning; TBI, total body irradiation

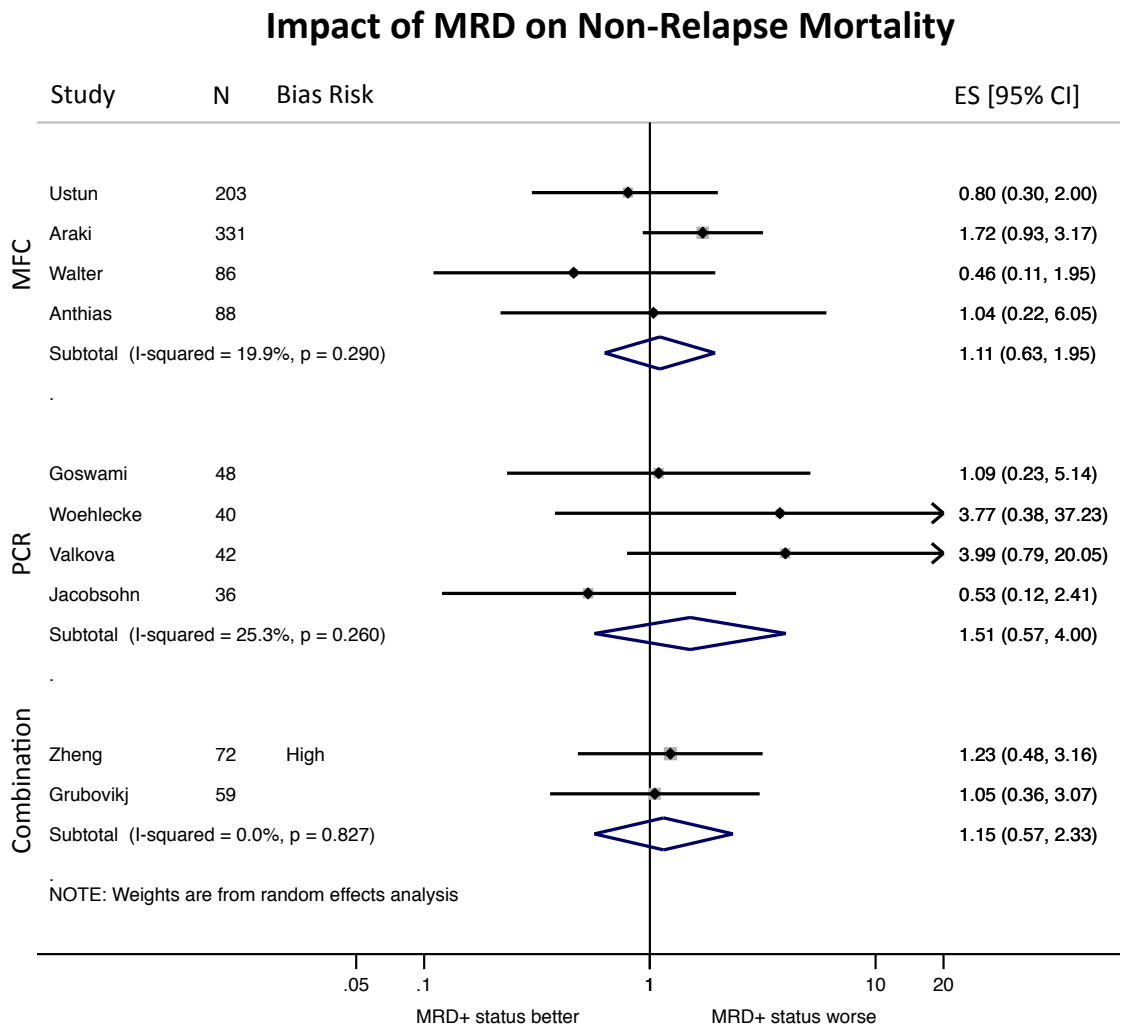
Supplemental Figure 1: Forest plot showing hazard ratio (effect size, ES) for overall survival with pooling of results for each MRD detection method. Columns indicate study size (N) and whether each study carries a high risk of bias (Bias Risk). Within each section, studies are listed by year of publication.



Supplemental Figure 2: Forest plot showing hazard ratio (effect size, ES) for cumulative incidence of relapse with pooling of results for each MRD detection method. Columns indicate study size (N) and whether each study carries a high risk of bias (Bias Risk). Within each section, studies are listed by year of publication.



Supplemental Figure 3: Forest plot showing hazard ratio (effect size, ES) for non-relapse mortality with pooling of results for each MRD detection method. Columns indicate study size (N) and whether each study carries a high risk of bias (Bias Risk). Within each section, studies are listed by year of publication.



Supplemental Figure 4: Forest plot showing hazard ratio (effect size, ES) for leukemia-free survival with pooling of results for studies using predominantly myeloablative and exclusively non-myeloablative conditioning strategies. Columns indicate year of publication (Year), study size (N), and method of MRD detection (Method).