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Selecting the Optimal Unrelated Hematopoietic Stem Cell Transplant Donor for Relapse Prevention in Acute Myeloid Leukemia

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Background

- Natural killer (NK) cells are lymphocytes belonging to the innate immune system which provide alloreactive graft versus leukemia (GVL) effect via germline encoded receptors including killer like immunoglobulin Receptors (KIR)
- NK cells can produce GVL in an HLA matched environment through KIR mediated interactions
- Effect of NK cell reconstitution kinetics on clinical outcomes in patients are not well studied

Objectives

- Validate a score based on the net known KIR-KIRL interactions for a given donor-recipient pair
- Examine the effect component KIR-KIR Ligand (KIRL) interactions and KIR-KIRL scores have on HSCT outcomes

NK Cell Function

- NK cells effector function is regulated by a balance of inhibitory and activating signals
 - KIR interact with HLA and HLA like molecules
 - A large inhibitory signal leaves the NK cell anergic and the target cell is tolerated
 - A large activating signal leads to target cell death through interferon gamma, perforin and granzyme production

Methods

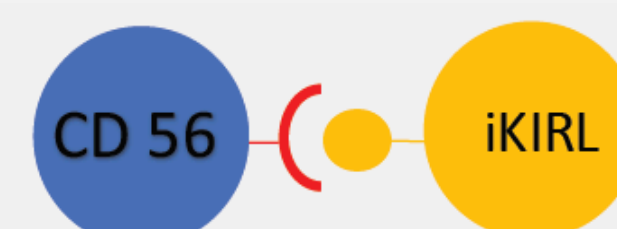
- Deidentified demographic and clinical outcomes data, as well as HLA and donor KIR genotyping information for this study were provided by the Center for International Blood and Marrow Transplant Research (CIBMTR, Milwaukee, WI)
- KIR component scores and the IM KIR Score were calculated as previously described and outlined in brief below

$$\text{aKIR Component Score} = (aKIR * aKIRL) = (+1 * +1) = |+1| = 1$$



Donor cell with activating KIR (aKIR) and recipient cell with corresponding HLA ligand

$$\text{iKIR Component Score} = (iKIR * iKIRL) = (-1 * +1) = |-1| = 1$$



Donor cell with Inhibitory KIR ligand (iKIR) and recipient cell with corresponding HLA ligand

$$\text{mKIR Component score} = (iKIR * mKIRL) = (-1 * -1) = |+1| = 1$$



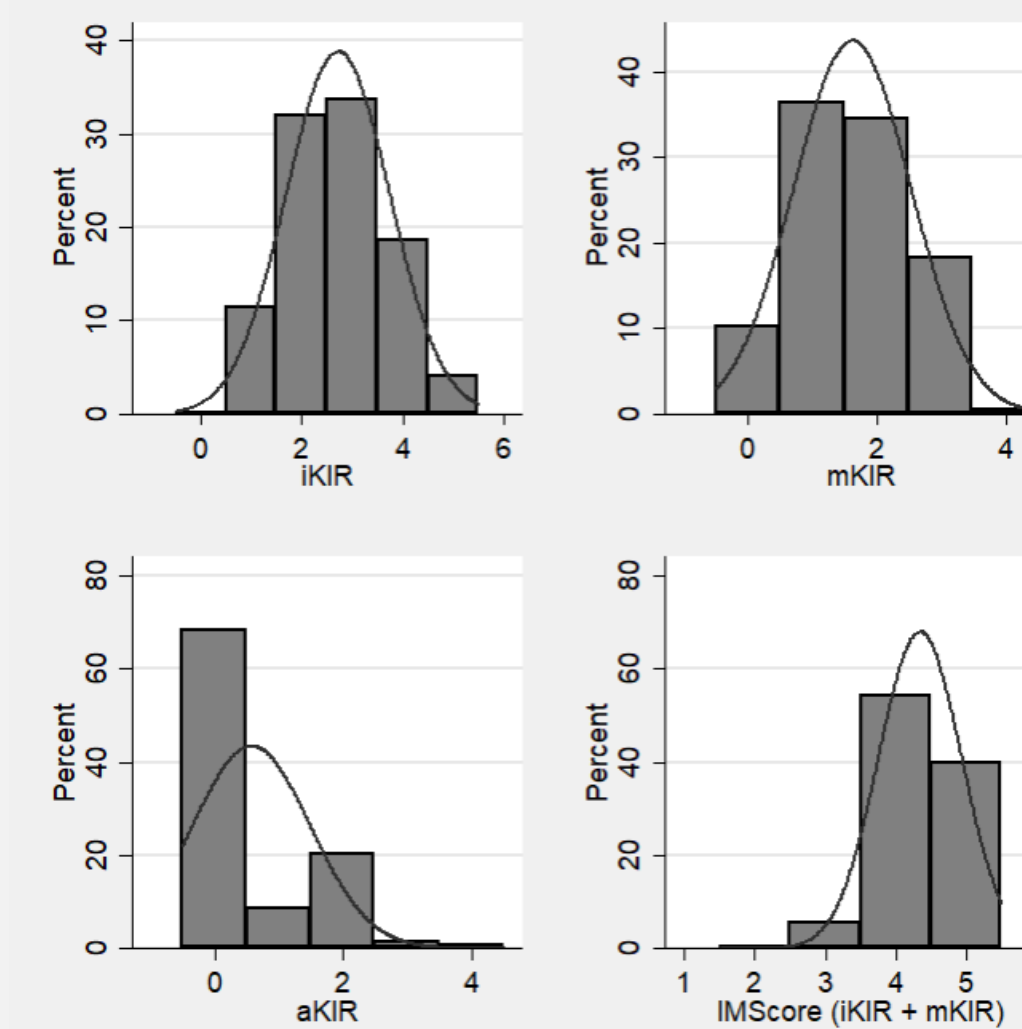
Donor cell with iKIR and recipient cell without corresponding HLA ligand (missing ligand)

$$\text{Inhibitory Missing Ligand (IM) KIR-KIRL Score} = |iKIR| + |mKIR|$$

Demographics

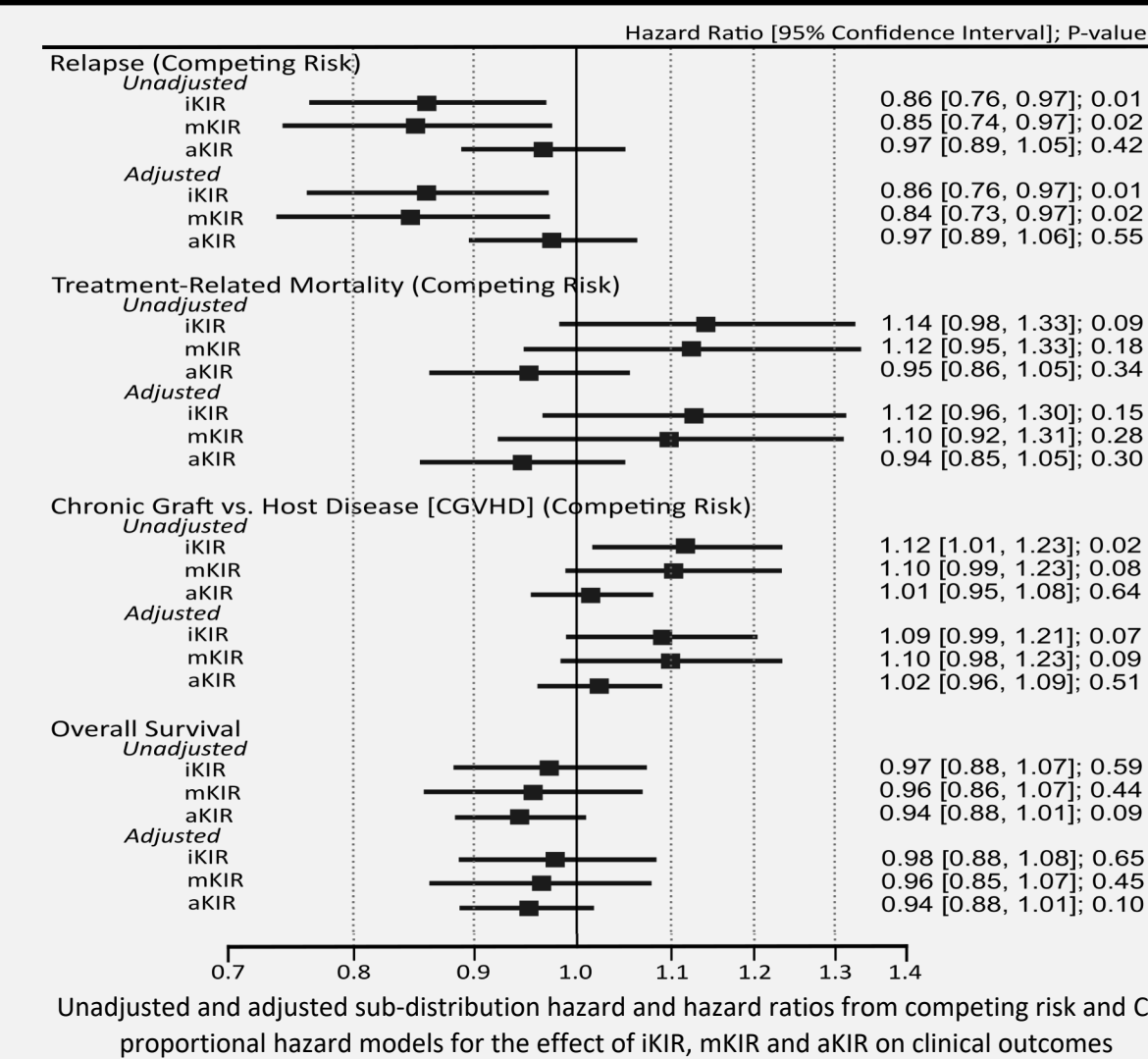
- 2365 DRPs transplanted for AML between 2010 and 2016 at 113 centers across the United States for AML
- This cohort included adults aged 20-83 years; 85% of DRPs were high-resolution 8/8 HLA-matched
- All patients received T cell replete grafts; 42% received *in vivo* T cell depletion
- The majority received a graft of mobilized peripheral blood stem cells (PBSC), 86% and 59% received myeloablative conditioning.
- During the 1,965,798 person-day follow up, 747 patients relapsed and 1,175 patients died

Population frequencies of KIR-KIRL interaction scores for inhibitory KIR (iKIR), missing KIRL (mKIR), activating KIR (aKIR) and IM-KIR scores.



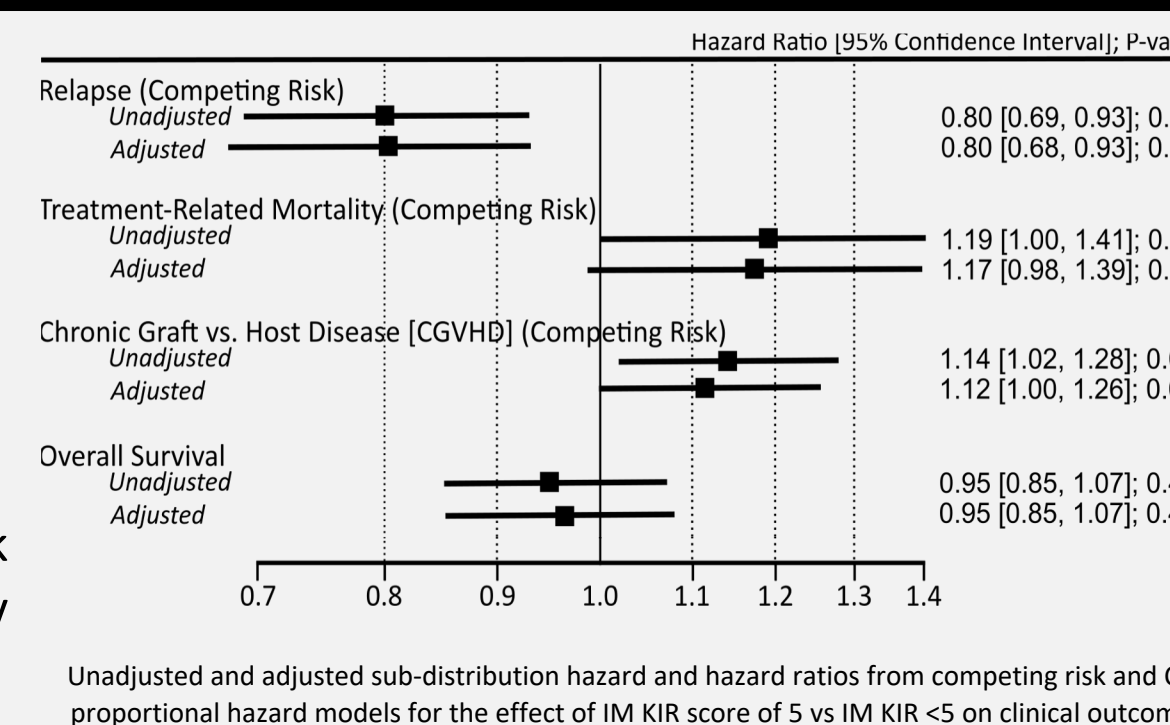
KIR KIRL Component Scores

- Higher iKIR and mKIR scores, were significantly associated with a reduced risk of AML relapse
- iKIR had a small impact on increasing the risk of cGVHD in unadjusted analysis, however this effect was not independent of the confounding variables included in the multivariate model
- As previously published aKIR associated with their known HLA ligand did not effect outcomes

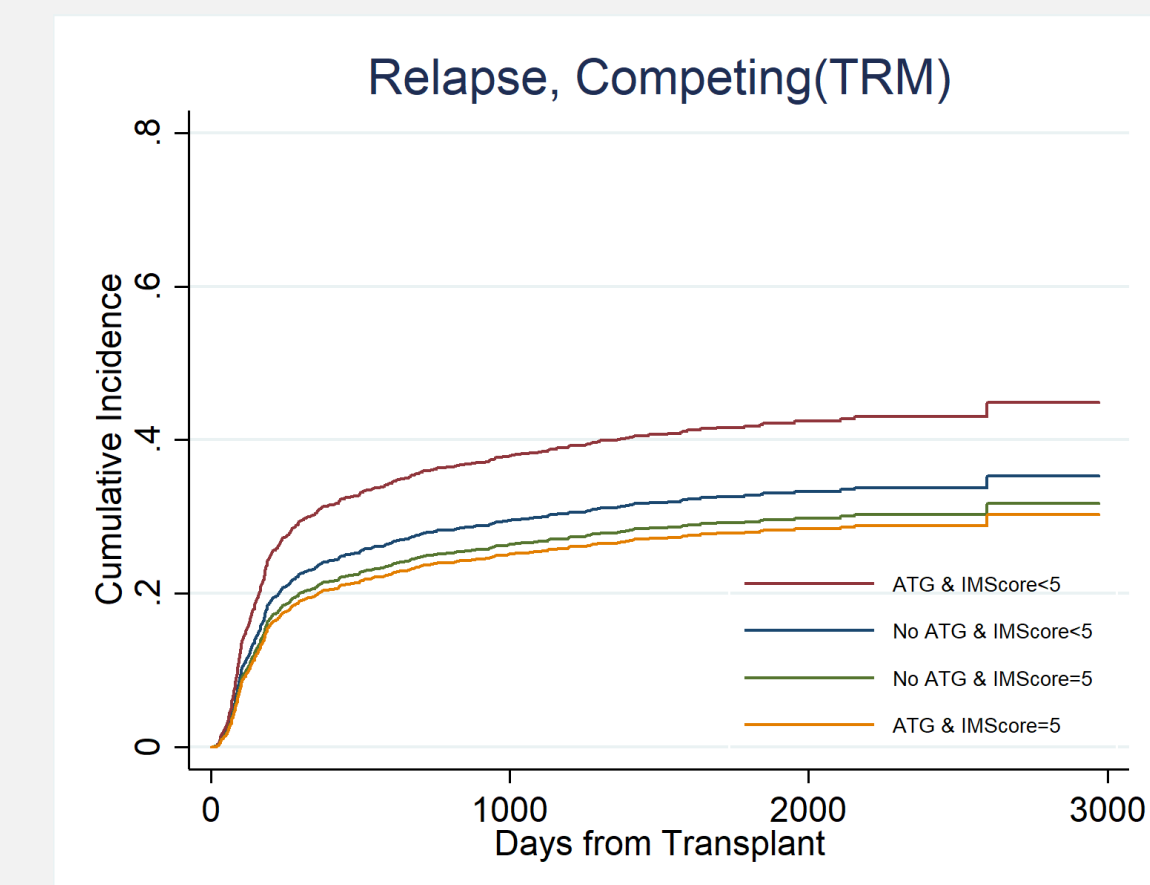


IM KIR Score

- Given their independent predictive value for relapse following URD HCT, the cumulative effect of iKIR and mKIR component scores was then examined with the IM-KIR score
- An IM KIR score of 5 (IM=5) decreased relapse risk by 20%
- Though this came at an increased risk of cGVHD and TRM; which most likely lead to lack of improvement of overall survival



The Effect of In Vivo T Cell Depletion



Unadjusted cumulative incidence curves by IM-KIR scores and *in vivo* T cell depletion with ATG depicting relapse.

- A subset of 8/8 HLA matched grafts (n=1958) were next examined to remove the confounding effects of HLA mismatch on clinical outcomes.
- Seven hundred and thirty of these patients received ATG for *in vivo* T cell depletion
- Recipients who received ATG and IM=5 saw a 39% relapse reduction (SHR 0.61 95% CI 0.46, 0.81, P=0.001)
- Interaction analysis indicated DRPs with an IM=5 donor, when administered ATG, did not experience the increased relapse risk seen in IM<5 DRP who received ATG (interaction P=0.049)

Discussion

- This large nationwide cohort validates our previous findings that the magnitude of iKIR and mKIR, as well as their combined IM KIR Score components are correlated with relapse risk after HCT for AML
- This challenges the notion that KIR are irrelevant to donor selection, and raises the question that those donors with the highest IM KIR scores in an appropriate transplant setting, may be considered as optimal donors for HCT recipients with AML to allow for increased NK cell mediated alloreactivity.
- Future clinical trials evaluating donor selection for URD HCT should include this measure to evaluate its value prospectively in uniformly treated patient cohorts
- Areas of further research
 - Extrapolating the HLA-KIR interaction scoring system to haploidentical and sibling transplant settings
 - Functional assessment of KIR reconstitution after HSCT
 - Quantification of NK cell IFN gamma production based on KIR-KIRL scores