

Background

Natural killer (NK) cells are involved in innate immune responses and play a major role in tumor surveillance, defense against viruses and in graft-versus-tumor effect after stem cell transplant.

NK cell activating or inhibitory functions are regulated by killer cell immunoglobulin like receptor (KIRs) and their ligands, which are HLA class I molecules. Seventeen KIR genes encode for receptors that can be activators or inhibitors. KIRs haplotype are categorized based on their gene content.

Objective

The aim of this study was to evaluate the relevance of KIR genotype in a series of patients with hematologic malignancies submitted to haploidentical SCT.

Materials & Methods

DESIGN: Retrospective cohort.

SETTING: Single-center study in a private referral hospital.

PATIENTS OR OTHER PARTICIPANTS: Donors of any age and adult patients with a diagnosis of AML or MDS; 17 patients underwent Haploidentical-SCT and 18 patients unrelated histoidential-SCT, from 2015 to 2020. KIR genotype was assessed in donors.

MAIN OUTCOMES MEASURES: The association of KIR genotype and OS, RFS, EFS and GVHD (III/IV and/or chronic). We consider patient ligands, donor KIR haplotype, B content, KIR inhibitor mismatches, presence of KIR2DS1 or KIR3DS1, activating KIRs matches, mismatching in KIR-ligands and the KIR-score. Secondary outcomes included KIR haplotype and GVHD and the association of KIR2DS2, KIR2DS4, KIR2DL2 mismatch and KIR3DL2 with cytomegalovirus (CMV) reactivation.

Results

Thirty-five patients and donors were included, median follow-up was 388 days. Median patient age was 51 years (range 19-71), median donor age was 32 years (range 13-48). Diagnoses were AML (n=30) and SMD (n=5). One-year OS was 64% in haploidentical-SCT and 80% In unrelated histoidential-SCT.

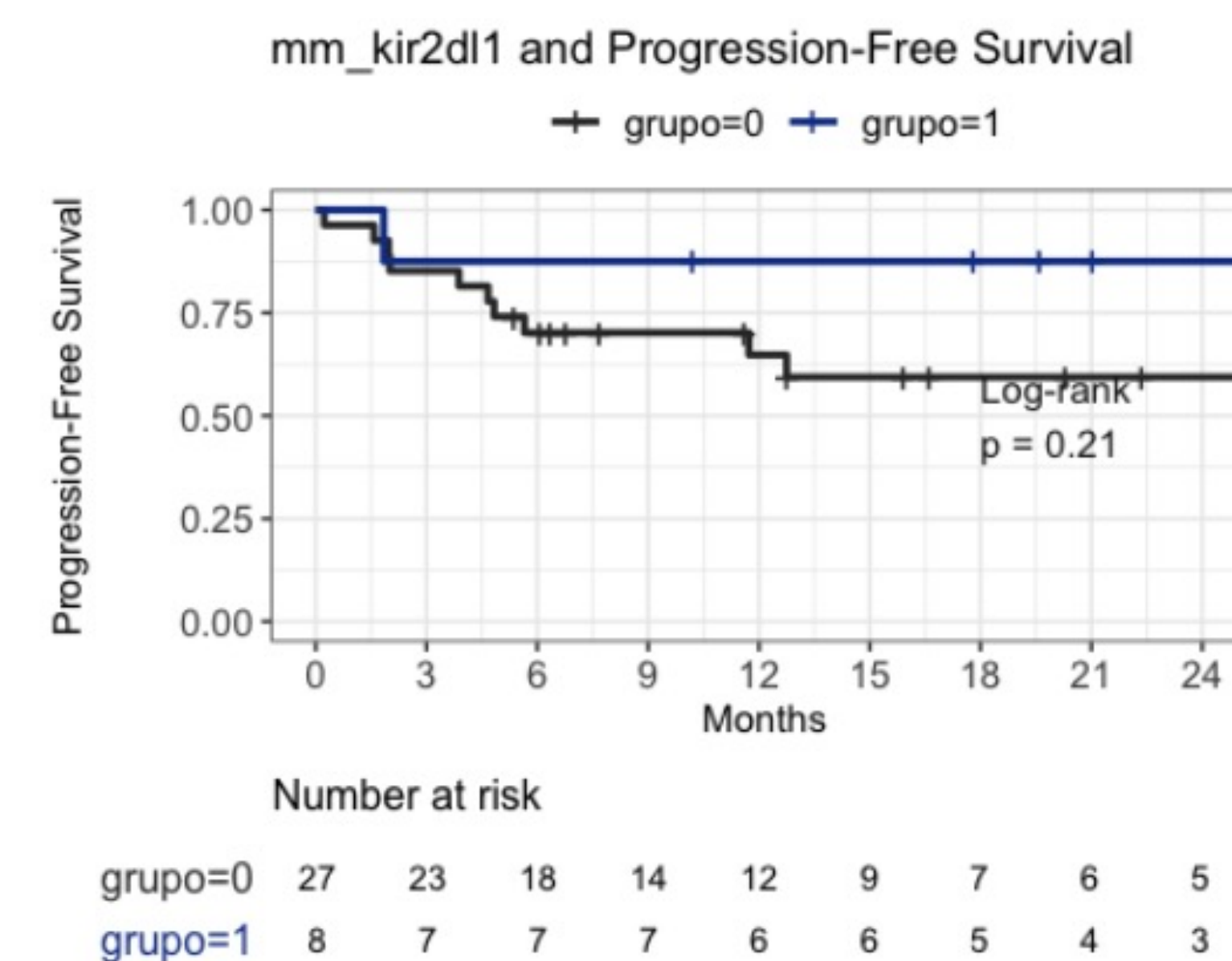
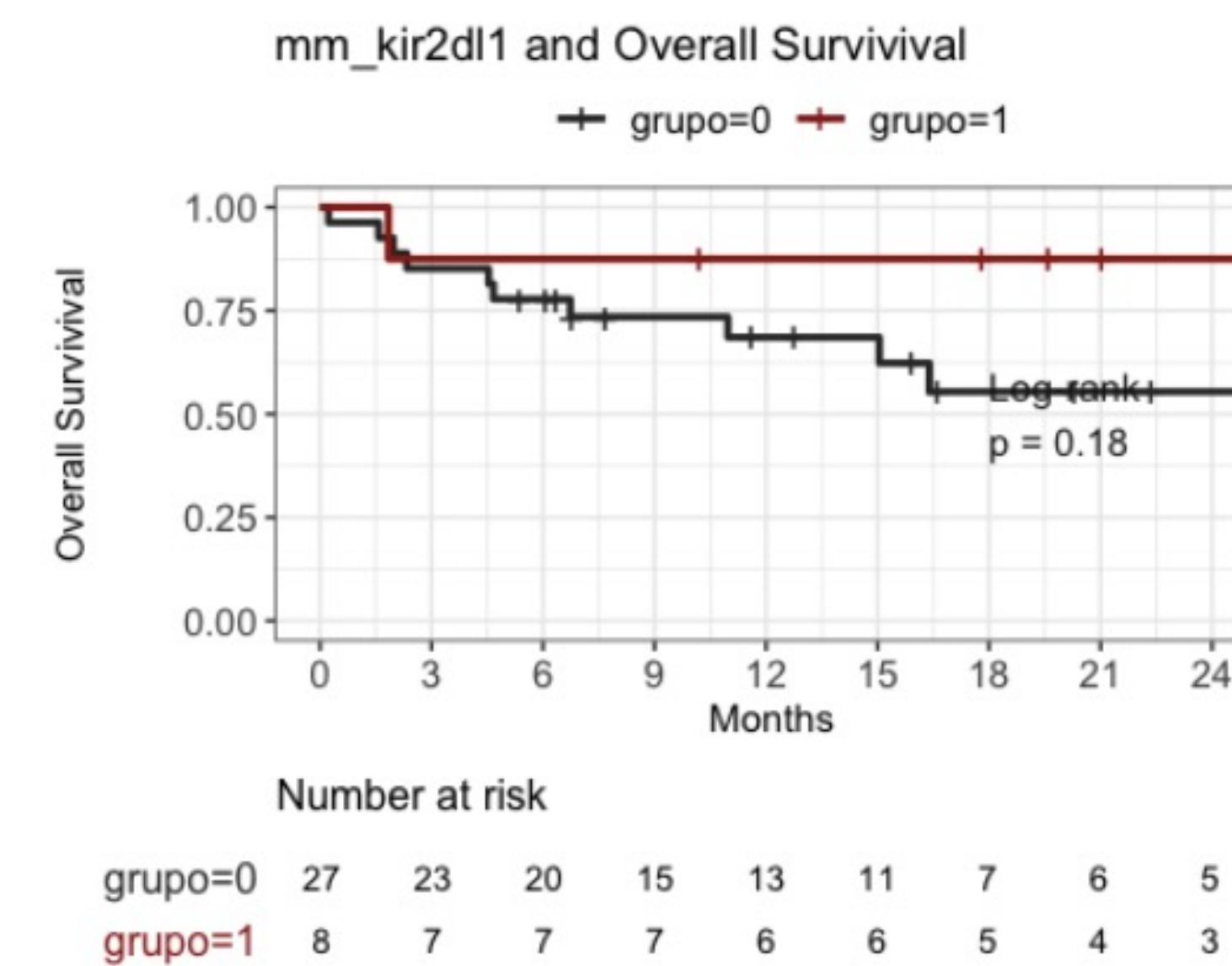
Table 1. Demographic Data and KIR Genotype Characteristics of Donors and Recipients, n (%)

Number of patients (%) Cohort (n=35)			
Patient age, y, median (range)	51 (19-71)	TBI	13 (36%)
Donor age, y, median (range)	32 (13-48)	Conditioning intensity	
Male recipient	20 (55%)	RIC	21 (60%)
Haplo-SCT	17 (49%)	MAC	14 (40%)
Diagnosis		Response before transplantation	
AML	30 (86%)	Complete	28 (80%)
MDS	1 (3%)	Partial	7 (20%)
MDS/MPS	4 (11%)	Donor KIR haplotype	
HCTI		AA	7 (20%)
0	17 (50%)	Bx	28 (80%)
1	4 (11%)	Donor B KIR content	
2	4 (11%)	Neutral	23 (76%)
3	8 (22%)	Better	6 (17%)
4	2 (6%)	Best	6 (17%)
KIR, killer cell immunoglobulin like receptor; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; MPS, myeloproliferative syndrome; RIC, reduced-intensity conditioning; MAC, myeloablative conditioning.			

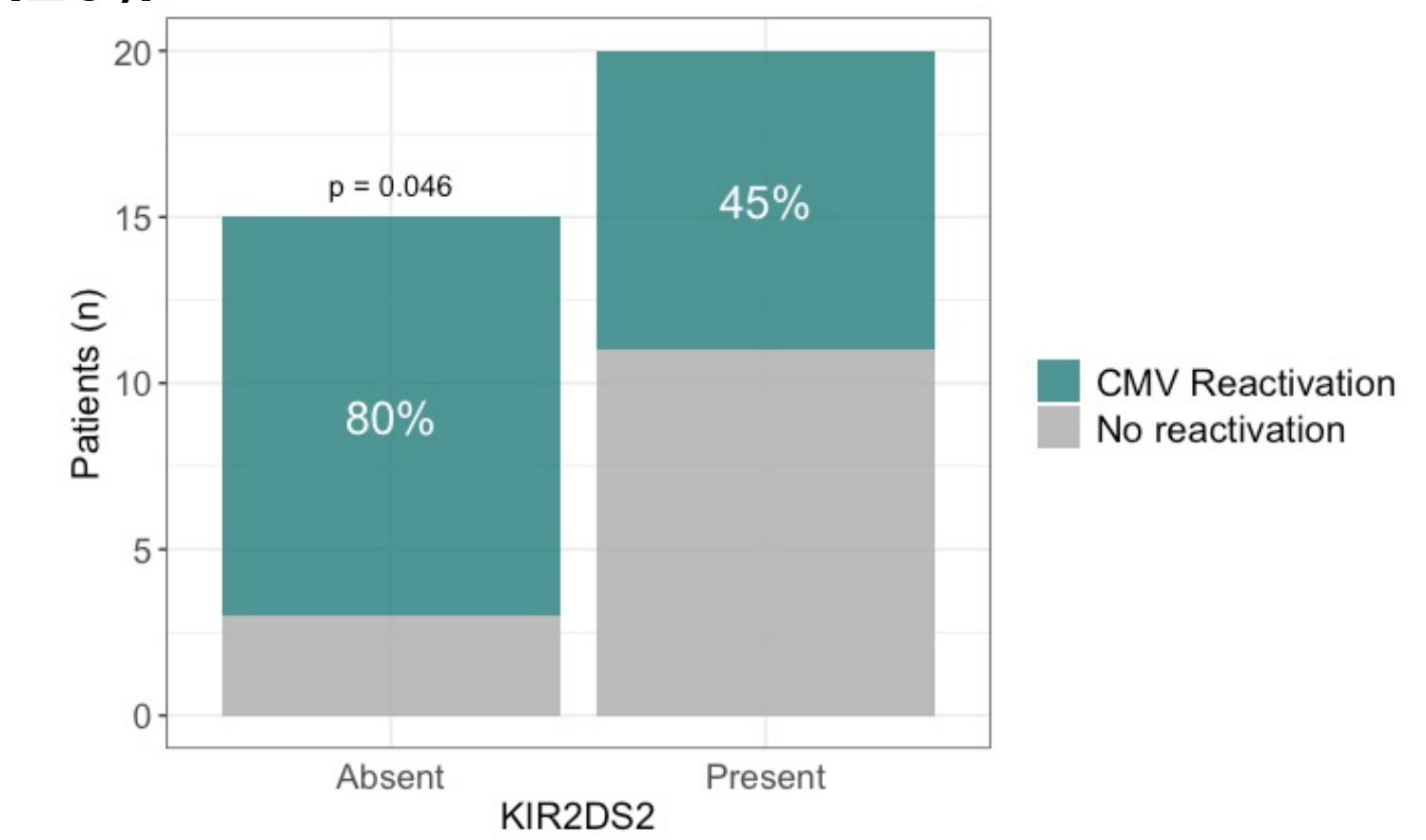
KIR genotype was Bx in 75% of donors. KIR2DL1-mismatch was associated with non-significant improvements in 2-year OS (84% vs 55%, p 0.18) and PFS (84% vs 60%, p=0.21).

Regarding mismatches of KIR ligands, the presence of mismatches in the GvH direction was associated with an increased risk of GVHD (50% vs 14%; P 0.08).

Fig 1 Missmatche-KIR2DL1 and OS (A) PFS (B)



The absence of KIR2DS2 gene resulted in a higher risk of CMV reactivation, 80% (12/15) vs. 45% (9/20) in the KIR2DS2 positive group (p = 0.005). Patients with CMV reactivation had a trend to higher incidence of GVHD (28% vs 7%,p=0.20).



Discussion

KIR genotyping can provide useful information. The presence of KIR2DS2 in the donor genotype identified a group of HCT patients at low risk for CMV reactivation. Larger cohort studies are needed to confirm these findings.

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References

- Torio A, Pascual MJ, Vidales I, Ortiz M, Caballero A, Heiniger AI. Donor Selection Based on Killer Cell Immunoglobulin–Like Receptor (KIR) Genotype May Improve Outcome After T-Cell–Replete Haploidentical Transplantation. Transplant Proc. 2018;50: 679–682.
- Robinson J, Waller MJ, Stoehr P, Marsh SGE,IPD-the Immuno Polymorphism Database ,Nucleic Acids Research (2005), 331:D523-526
- Krieger E, Sabo R, Moezzi S, Cain C, Roberts C, Kimball P, et al. Killer Immunoglobulin-Like Receptor-Ligand Interactions Predict Clinical Outcomes following Unrelated Donor Transplantations. Biol Blood Marrow Transplant. 2020;26: 672–682.
- Zaia J.A., Sun J.Y., Gallez-Hawkins G.M., Thao L., Oki A., Lacey S.F., Dagis A., Palmer J., Diamond D.J., Forman S.J., et al. The effect of single and combined activating killer immunoglobulin-like receptor genotypes on cytomegalovirus infection and immunity after hematopoietic cell transplantation. Biol. Blood Marrow Transplant. 2009;15:315–325. doi: 10.1016/j.bbmt.2008.11.030.