

1 **Title**

2 Presence of donor-encoded centromeric KIR B content increases the risk of infectious mortality in
3 recipients of myeloablative, T cell deplete, HLA-matched HCT to treat AML

4

5 **Running title**

6 Donor Cen-B increases NRM in matched adult MAC AML patients

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24

1 **Abstract**

2 The reported influence of donor Killer-cell Immunoglobulin-like Receptor (KIR) genes on the
3 outcomes of haematopoietic cell transplantation (HCT) are contradictory, in part due to diversity of
4 disease, donor sources, era and conditioning regimens within and between different studies. Here, we
5 describe the results of a retrospective clinical analysis establishing the effect of donor KIR motifs on
6 the outcomes of 119 HLA-matched, unrelated donor HCT for adult acute myeloid leukaemia (AML)
7 using myeloablative conditioning (MAC) in a predominantly T cell deplete (TCD) cohort. We observed
8 that HCT involving donors with at least one KIR B haplotype were more likely to result in non-relapse
9 mortality (NRM) than HCT involving donors with two KIR A haplotypes ($p=0.019$). Upon separation
10 of KIR haplotypes into their centromeric (Cen) and telomeric (Tel) motif structures, we demonstrated
11 that the Cen-B motif was largely responsible for this effect ($p=0.001$). When the cause of NRM was
12 investigated further, infection was the dominant cause of death ($p=0.006$). No evidence correlating
13 donor KIR B haplotype with relapse risk was observed. The results from this analysis confirm previous
14 findings in the unrelated, TCD, MAC transplant setting and imply a protective role for donor-encoded
15 Cen-A motifs against infection in allogeneic HCT recipients.

16

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20

21 **Author statement**

22 None of the authors declare any conflicts of interest.

23

1 **Introduction**

2 Despite developments in the treatment of patients with haematological malignancies to specifically
3 target diseased cells, achieving long term remission in adult acute myeloid leukaemia (AML) remains
4 challenging and haematopoietic cell transplantation (HCT) continues as the mainstay of treatment for
5 high risk patients¹. Selection of volunteer unrelated donors (VUD) for allogeneic HCT is primarily
6 based on HLA allele matching at the HLA-A, -B, -C, -DRB1 and -DQB1 loci, although many centres
7 have also recently adopted a permissible matching model including the HLA-DPB1 locus²⁻⁵. However,
8 even in recipients of well-matched grafts, five year overall survival (OS) remains <50%, with both
9 relapse and death from transplant-related complications remaining significant problems^{1, 6}. As such,
10 investigation into secondary donor characteristics have been performed and confirmed the importance
11 of non-HLA factors, particularly donor age and CMV matching, in reducing non-relapse mortality
12 (NRM)^{4, 7, 8}.

13

14 In addition to these secondary donor characteristics, selection of donors for non-HLA genetic factors
15 has also been explored as a method to improve HCT outcomes. The Killer-cell Immunoglobulin-like
16 Receptors (KIR), predominantly expressed on the surface of natural killer (NK) cells, are amongst the
17 most promising non-HLA candidate gene families. KIR form a family of activating and inhibitory
18 receptors which, upon binding their cognate HLA ligand, may elicit, or inhibit, an immune response.
19 The genes encoding these proteins can be grouped into two main haplotypes: KIR A haplotypes are
20 conserved in gene content and encode only one activating KIR gene (KIR2DS4) in combination with
21 multiple inhibitory genes (KIR2DL1, KIR2DL3, KIR2DL4, KIR3DL1, KIR3DL2 and KIR3DL3). By
22 contrast, KIR B haplotypes have a more variable gene content and encode at least one of the alternative
23 KIR genes⁹. In addition, KIR haplotypes may be further defined according to their centromeric (Cen)
24 or telomeric (Tel) gene motifs¹⁰.

25

26 The relevance of KIR-mediated immunity in HCT to treat AML was first discovered by investigating
27 disparity between donor and recipient inhibitory KIR ligands, subsets of HLA class I molecules

1 encoding the HLA-C1, -C2 and -Bw4 motifs, in haploidentical T cell-depleted (TCD)
2 transplantations¹¹. Ruggeri *et al.* (2002)¹², demonstrated protection from disease relapse without
3 concurrent increase in frequency of graft *versus* host disease (GVHD) in AML recipients whose grafts
4 were derived from donors possessing KIR ligands that were not present in the recipient, often referred
5 to as “missing self”. As such, they proposed that graft *versus* leukaemia (GVL) alloreactivity could be
6 mediated by donor NK cells when KIR ligand disparity was present. Importantly, this effect appeared
7 to be limited to AML recipients as the same effect was not observed in acute lymphoblastic leukaemia
8 (ALL) patients. Following this, several studies have confirmed this model in haploidentical and other
9 HLA-mismatched allogeneic transplant settings^{13,14}.

10

11 In addition to relapse and GVHD, infection remains a major contributor to the high mortality rates
12 associated with HCT. In addition to *de novo* infections acquired during the extended periods of
13 immunosuppression, viral reactivation is also a common cause of morbidity and mortality. In the UK,
14 frequent use of TCD as GVHD prophylaxis, often utilising alemtuzumab, may exacerbate this issue¹⁵.
15 NK cells are the first lymphocyte subset to reconstitute following HCT and are known to target virally-
16 infected cells. However, NK cell reactivity resulting from KIR-ligand mismatching has, in contrast to
17 its findings in relapse, been proposed to increase patients’ susceptibility to infection-related mortality¹⁶,
18 ¹⁷.

19

20 Although mismatches between donor and recipient KIR ligands are not possible in HLA-matched
21 transplants, KIR-mediated alloreactivity may still exist, as donor NK cells may express inhibitory KIR
22 specific for ligands that are not encoded by either the patient or donor. This represents a “missing
23 ligand” condition that has been shown to increase the risk of acute GVHD (aGVHD) but decrease the
24 risk of relapse, ultimately increasing OS and disease-free survival (DFS)¹⁸⁻²³. In addition, there are KIR
25 molecules whose ligands are yet to be defined which may also permit KIR-mediated alloreactivity.

26

27 The most recent KIR-mediated alloreactivity model has been proposed based on findings from a large
28 cohort of T cell replete, myeloablative conditioning (MAC) transplants. Using this model, a scale of

1 alloreactivity is established based on the activating KIR content of the graft, reflected by the donor's
2 KIR haplotypes. This has shown that OS can be increased by selecting donors who encode at least one
3 copy of the KIR B haplotype (KIR Bx)²⁴. Upon further investigation, it was discovered that Cen-B
4 motifs were predominantly associated with this outcome, and their presence correlated with a
5 significant reduction in relapse and improved DFS, particularly in HLA-C mismatched transplants
6 where the recipient encodes the HLA-C1 ligand^{10,25}. However, when a similar comparison investigating
7 Cen motifs was performed in a large cohort of transplants utilising reduced intensity conditioning (RIC)
8 regimens, no significant difference was observed^{18,20}.

9

10 The effect of KIR genotype polymorphism on HCT outcomes is therefore controversial and appears
11 highly dependent on a variety of transplant characteristics. To reduce heterogeneity within the cohort,
12 this study focusses only on the outcomes of a specific group of HCT recipients: TCD, HLA-matched,
13 adult, myeloablative transplants to treat AML. Thereafter, we have investigated the influence of donor
14 KIR genotypes on the outcomes of HCT within this UK cohort.

15

16 **Materials and Methods**

17 *Study cohort*

18 One hundred and nineteen HCT recipients and their respective VUDs were included in this study. All
19 transplants took place between December 1996 and June 2011. Transplant inclusion criteria were as
20 follows: i) UK-based adult transplanted to treat AML, ii) MAC regimen, iii) stem cells provided from
21 an Anthony Nolan VUD and iv) complete allele-level HLA matching for HLA-A, -B, -C, -DRB1 and
22 -DQB1, as described previously²⁶. Clinical outcomes data were obtained in collaboration with the
23 British Society of Blood and Marrow Transplantation. Ethical approval was obtained from the National
24 Research Ethics Service (www.nres.nhs.uk, application number: MREC 01/8/31). The project was
25 approved by Anthony Nolan medical and scientific committees. Informed consent was obtained from
26 all participants prior to donation of blood or buccal cell samples for genetic analysis.

27

1 *DNA extraction*

2 Genomic DNA was extracted from whole blood or buccal swab samples. When extracted from blood,
3 DNA was obtained either from salting-out²⁷ or paramagnetic bead-based DNA purification (Promega,
4 Madison, WI, USA). When extracted from buccal swabs, DNA was obtained using Genra Puregene
5 Buccal Cell Kit (QIAGEN, Hilden, Germany).

6
7 *KIR genotyping*

8 Briefly, presence or absence of 16 individual KIR genes was analysed using a polymerase chain reaction
9 sequence-specific priming (PCR-SSP) approach described previously²⁸. No distinction was made
10 between the presence of KIR2DL5A or KIR2DL5B. The presence of at least one KIR B haplotype-
11 specific locus indicated that the genotype contained at least one B haplotype. Such samples were
12 depicted as KIR Bx. All samples that lacked the presence of all KIR B loci were assigned the AA
13 genotype designation (KIR AA). Centromeric (Cen) and telomeric (Tel) gene motifs were assigned as
14 described previously¹⁰. HLA-C1, -C2 and -Bw4 epitope ligands for KIR molecules were inferred from
15 previous HLA typing.

16
17 *Statistical analysis*

18 Survival and DFS probability curves were calculated by the method of Kaplan-Meier²⁹. Groups were
19 compared using the log-rank test, whilst multivariate analysis was performed by Cox regression³⁰.
20 Several analyses incurred competing risks. The competing risk in relapse analysis was non-relapse
21 mortality (NRM), whilst relapse was the competing risk in NRM analysis. When comparing the risk of
22 infectious mortality between different groups, relapse or death due to any other cause were the
23 competing risks. For these competing risk analyses, univariate probabilities were calculated using the
24 cumulative incidence function³¹. Multivariate competing risk analysis was performed using the method
25 by Fine and Gray³². A forward stepwise selection of covariates for multivariate analysis was performed
26 using $p \leq 0.05$ inclusion criteria. Statistical significance was denoted at $p \leq 0.05$, whilst statistical trend
27 was signified by $p \leq 0.1$. All univariate and multivariate analyses were performed using 'R' software
28 (version 3.4.2).

1

2 **Results**

3 *Patient and donor characteristics*

4 Donor and recipient demographics and HCT conditions are given in Table 1. Of the 84 donors encoding
5 at least one KIR B haplotype, 65 encoded at least one Cen-B motif (Cen-Bx, Figure 1). The remaining
6 54 donors (45%) encoded only Cen-A haplotype motifs (Cen-AA). When comparing the Cen-AA and
7 Cen-Bx donor groups, the only statistically significant difference was between donor-recipient gender
8 matching, by which gender-matched transplants were more likely to utilise Cen-Bx donors. As donor
9 KIR genotyping was not performed prior to donor selection, this criterion was not knowingly selected.
10 No other significant differences in clinical or prognostic factors were observed between those
11 transplants using donors encoding Cen-AA or Cen-Bx.

12

13 For the whole cohort, the probabilities of survival and relapse at five years post-transplant were 38.6%
14 and 34.5% respectively, whilst the probability of NRM at one year post-transplant was 23.0%. All such
15 univariate analyses were performed using methods of Kaplan-Meier and cumulative incidence as
16 described in the Materials and Methods. When assessing the impact of the clinical variables on these
17 outcomes of HCT, several factors demonstrated trends and borderline significance with detrimental
18 outcomes. Older recipients (>40 years) had decreased OS at five years post-transplant ($p=0.049$), as did
19 recipients with a history of previous autografts ($p=0.028$).

20

21 *Presence of donor KIR B haplotypes increase incidence of non-relapse mortality*

22 Univariate analysis of the effect of donor KIR haplotypes on the outcomes of HCT associated the
23 presence of donor-encoded KIR B haplotype with an increase in the incidence of NRM after one year
24 post-transplant (KIR AA: 9%, 95% confidence interval [CI]=2.9-26.1 vs KIR Bx: 29%, CI=20.6-40.6;
25 $p=0.019$; Figure 2A, Table 2). This increase in NRM was associated with statistical trends towards
26 decreased OS (KIR AA: 49%, CI=34.5-69.4 vs KIR Bx: 34%, CI=25.4-46.6; $p=0.06$) and DFS (KIR
27 AA: 46%, CI=32.2-66.9 vs KIR Bx: 31%, CI=22.5-43.4; $p=0.087$) at five years post-transplant.

1 Interestingly, despite most previous analyses implicating KIR-mediated differences in relapse risk, no
2 statistically significant differences were observed in this dataset (Table 2).

3
4 Following the observation that the presence of donor KIR B haplotypes was associated with increased
5 NRM probability, donor genotypes were stratified by their Cen and Tel motif patterns. Outcomes in
6 patients receiving HCT from donors encoding the Tel-Bx motif were not associated with any difference
7 when compared to Tel-AA donor transplants (Table 2). Presence of the Cen-B motif within donors,
8 however, was associated with a significant increase in the probability of NRM at one year post-
9 transplant (Cen-AA: 9%, CI=4.0-21.7 vs Cen-Bx: 34%, CI=24.4-48.4; p=0.001, Figure 2B). This
10 observation correlated with significantly improved five year OS (Cen-AA: 48%, CI=35.7-63.7 vs Cen-
11 Bx: 31%, CI=21.6-45.1; p=0.024) and DFS (Cen-AA: 45%, CI=32.9-60.5 vs Cen-Bx: 29%, CI=19.3-
12 42.6; p=0.045, Table 2). In a multivariate regression analysis, the significant difference between
13 outcomes of Cen-AA and Cen-Bx donor transplants was preserved (OS: Cen-Bx hazard ratio [HR]=1.9,
14 CI=1.2-3.1, p=0.01; NRM: Cen-Bx HR=4.2, CI=1.6-11.0, p=0.004, Table 3).

15
16 When compared to the Cen-AA motif structure, the impact of each additional Cen-B motif was also
17 assessed. This revealed a dose effect, whereby the more copies of donor-encoded Cen-B motif, the
18 higher the risk of NRM at one year post-transplant (Cen-AA: 9%, CI=4.0-21.7 vs Cen-AB: 33%,
19 CI=22.0-48.5 vs Cen-BB: 42%, CI=20.5-84.8; p=0.005, Figure 3A). This corresponded with significant
20 differences in OS (Cen-AA: 48%, CI=35.7-63.7 vs Cen-AB: 37%, CI=25.7-52.7 vs Cen-BB: 8%,
21 CI=1.3-54.4; p=0.01, Figure 3B) and DFS (Cen-AA: 45%, CI=32.9-60.5 vs Cen-AB: 34%, CI=22.9-
22 49.8 vs Cen-BB: 8%, CI=1.3-54.4; p=0.031, Table 2) at five years post-transplant.

23

24 *Cause-of-death analysis implicates donor Cen-B with impaired viral protection*

25 To further investigate how donor-encoded centromeric motif structure affects NRM risk, the 27
26 transplants resulting in NRM were stratified by cause-of-death. Infection was recorded as a cause-of-
27 death in 19 recipients, whilst GVHD was implicated in only five (cause-of-death in one recipient
28 included both GVHD and infection). One transplant resulted in NRM without infection or GVHD, and

1 data was missing for three further transplants. Accordingly, a competing risk analysis assessing the risk
2 of death by infection at one year between transplants utilising Cen-AA and Cen-Bx donors was
3 performed and revealed a strong protective effect of donor-encoded Cen-AA (Cen-AA: 6%, CI=1.8-
4 17.0 vs Cen-Bx: 25%, CI=15.8-38.4; p=0.006). This withstood multivariate analysis as the only
5 remaining statistically significant factor (Cen-Bx: HR=5.5, CI=1.5-20.3, p=0.011, Table 3). Of the 15
6 instances where data on the type of infection was available, 13 cases (87%) involved viral infection.

7 8 **Discussion**

9 The relevance of matching between donor and recipient HLA types has been well-documented and is a
10 key determinant of HCT success^{3, 4}. However, the KIR genotype of the donor, encoding receptors for
11 these hyperpolymorphic HLA, is not routinely considered in VUD selection. Previous studies in T cell
12 replete MAC cohorts have implicated donor-encoded Cen-B haplotype motif presence with a beneficial
13 reduction in relapse risk, leading to improved OS and DFS^{10, 25}. By contrast, the results obtained in this
14 predominantly TCD cohort fail to indicate any beneficial reduction in AML relapse associated with
15 donor-encoded Cen-B motifs, and instead implicate these motifs with increased NRM risk, leading to
16 decreased OS and DFS.

17
18 Although our findings contradict these apparently similar studies, the different T cell content between
19 the grafts may be responsible for the conflicting outcomes. These data may support an orchestrated role
20 for NK cell interaction with T cells³³, interpreted as innate NK cells playing a coordinating role for
21 early T cell reconstitution after transplant. This NK cell-T cell interaction is likely to be common to all
22 HCT, but the effects may be more apparent after TCD where T cell function is impaired or delayed. In
23 addition, our findings concur with the study by Kröger *et al.* (2006)¹⁷, whereby a higher number of
24 different activating KIRs encoded by the donor corresponded with increased NRM in a MAC, TCD
25 cohort. Furthermore, another study investigating the effect of TCD on KIR-mediated immunity
26 following HCT also observed elevated NRM as a result of increased infection-related mortality,

1 theorising the observation as a result of increased targeting of antigen-presenting dendritic cells by
2 activated NK cells^{16, 34}.

3
4 When the cause of death was investigated in the study presented here, infection, particularly viral
5 infection, was strongly associated with increased mortality in Cen-Bx donor transplants, whereas a
6 greater level of protection against infection-related mortality was offered by Cen-AA donors. This,
7 again, contrasts with studies in T cell replete transplants where increasing numbers of activating KIR,
8 and particularly KIR2DS2 (restricted to the Cen-B motif), were demonstrated to aid control of human
9 cytomegalovirus (CMV) reactivation³⁵. Viruses, such as CMV, display a range of functions aimed to
10 modulate NK cell reactivity, including the upregulation of expression of the inhibitory ligand, HLA-E³⁶,
11 as well as sequestration of activating ligands such as major histocompatibility complex class I
12 polypeptide-related sequence B (MICB)³⁷. However, viral downregulation of HLA class I antigen
13 expression, as a means of evading T cell-mediated immunity, can also stimulate NK cell activation via
14 the recognition of “missing-self”^{38, 39}. Licensed NK cells, which are more functional owing to
15 expression of at least one inhibitory receptor for a host-encoded HLA class I molecule, recognize the
16 lack of inhibition and mount an immune response.

17
18 The strong avidity offered by alleles of KIR2DL2/3 commonly located on the Cen-B haplotype motif
19 has been shown to correspond with functionally stronger licensing than KIR2DL2/3 alleles which tend
20 to reside on the Cen-A motif^{40, 41}. This increased level of licensing, when tested in cells lines that fail
21 to express any HLA class I on the cell surface, is capable of stimulating an increased response. However,
22 complete absence of HLA class I expression is unlikely to be environmentally plausible during viral
23 infection. As such, presence of high avidity Cen-B KIR2DL2/3 alleles in combination with
24 downregulated HLA-C may actually offer a greater level of inhibition than the equivalent interaction
25 between Cen-A KIR2DL2/3 alleles and downregulated HLA-C. The increased inhibition would require
26 a greater activating signal to supersede it, resulting in decreased NK cell reactivity. In addition, the
27 delayed reconstitution of KIR2DL1 following HCT may place additional burden on KIR2DL2/3
28 licensed NK cell immunity⁴². Differential NK cell inhibition via KIR2DL2/3 has also been proposed as

1 a theory to explain the observation that increasing copies of KIR2DL3-HLA-C1 (typically weak avidity
2 interactions) results in improved resolution of hepatitis C virus infection^{43, 44}. Additionally, evidence
3 that NK cell education via activating KIRs (such as those which define the Cen-B motif) renders NK
4 cells hyporesponsive may also indicate improved NK cell reactivity associated with the Cen-A
5 haplotype motif⁴⁵.

6
7 Several limitations to the study mean that the results must be approached with some caution. Although
8 care was taken to maximise cohort homogeneity, the retrospective, multicentre aspect of this study
9 introduces the caveat of variable transplant protocols and presented difficulties in collecting complete
10 clinical follow-up data, including those relating to co-morbidities and the types of viral infections that
11 occurred post-transplant. In addition, the era of transplants ranged considerably, from 1996 to 2011.
12 Amongst other factors, significant evolution of antiviral and antifungal agents has occurred over this
13 time period. Furthermore, the relatively small sample size and event incidence may be underpowered
14 to resolve some compound variables. The KIR locus itself introduces a range of complexities not
15 accounted for in this study. For example, the highly polymorphic nature of each KIR gene introduces
16 variety in the expression and functionality of each locus. The implementation of high resolution, allelic-
17 level KIR typing is warranted to resolve these issues in the future⁴⁶. Finally, the scope of this analysis
18 has been limited to only investigate the KIR-mediated aspect of immunity, ignoring other NK cell
19 receptor-ligand signalling pathways and alloreactivity mediated by T and B cells. Future, well-defined
20 prospective studies using uniform transplant conditions may help to clarify the effects of the
21 combinations of donor KIR and recipient ligands on HCT outcomes.

22
23 In summary, we have demonstrated that donor-encoded KIR genes can affect the NRM risk following
24 VUD HCT. Specifically, the presence of donor-encoded Cen-B haplotype motifs conveys a significant
25 risk of infectious mortality, which in turn equates to a significant reduction in OS. Multivariate analysis
26 adjusting for other transplant characteristics suggested that donor KIR centromeric genotype was the
27 only significant determinant for NRM risk. However, these findings may only be applicable to cases of
28 HLA-matched, unrelated donor, MAC, TCD transplants to treat adult AML, as differing HCT scenarios

1 have repeatedly generated contradictory findings, including observations in our own TCD, RIC cohort
2 (unpublished data). This highlights the important differences between transplant scenarios and suggests
3 that, when selecting donors based on KIR genotype information, it is unlikely that a ‘one-size-fits-all’
4 donor KIR genotype exists. Instead, these findings support the selection of VUDs based on KIR
5 genotype, but only when considered in parallel with other transplant factors.

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1 **Figure legends**

2 Figure 1: Charts demonstrating the proportions of different centromeric motif structures within donor
3 subgroups. Over 75% of KIR BX donors encode at least one Cen-B motif (Cen-BX, solid grey). The
4 remainder all encode two copies of the Cen-A motif (Cen-AA, dotted). Of the Cen-AA donors,
5 approximately one third encode the KIR BX genotype (hashed), whilst the remainder encode KIR AA
6 (striped).

7

8 Figure 2: Donor KIR B genotype increases NRM. A) Univariate probability of NRM at one year
9 post-transplant for groups based on the presence of at least one donor-encoded KIR B haplotype. This
10 demonstrates that a significant increase in NRM is associated with donors encoding the KIR BX
11 haplotype structure. B) When the haplotype structure is refined according to centromeric motif
12 structure, donor-encoded Cen-B appears culpable for the increase in NRM. As described in the footer
13 of Table 2, the total number of transplants included in this NRM analysis is one less than listed in Table
14 2 as a result of one transplant missing relapse data.

15

16 Figure 3: Effect of donor Cen-B is dose-dependent. A) Univariate probability of NRM at one year post-
17 transplant for groups based on donor-encoded Cen-B motif copy number. With each additional Cen-B
18 motif, risk of NRM increases. B) When OS is assessed with the same grouping strategy, the detrimental
19 effect of donor Cen-B is also evident. As described in the footer of Table 2, the total number of
20 transplants included in this NRM analysis is one less than listed in Table 2 as a result of one transplant
21 missing relapse data.

22

Table 1 – Recipient and donor demographics

Variable	Donor KIR Cen-AA	%	Donor KIR Cen-BX	%	P-value
Donor age, years					
Median (Range)	34 (20-49)		35 (19-60)		0.88
≤30	17	31.5	22	33.8	0.94
>30	37	68.5	43	66.2	
Recipient age, years					
Median (Range)	34 (18-64)		37 (18-67)		0.17
≤40	40	74.1	45	69.2	0.71
>40	14	25.9	20	30.8	
Donor sex					
Female	10	18.5	7	10.8	0.35
Male	44	81.5	58	89.2	
Recipient sex					
Female	22	40.7	24	36.9	0.81
Male	32	59.3	41	63.1	
Recipient-donor sex matching					
Matched	26	48.1	44	67.7	<i>0.049</i>
Mismatched	28	51.9	21	32.3	
Recipient-donor CMV					
Matched	43	79.6	48	73.8	0.57
Mismatched	10	18.5	16	24.6	
Missing	1	1.9	1	1.5	
Donor positive, Recipient positive	9	16.7	6	9.2	0.32
Donor positive, Recipient negative	0	0.0	4	6.2	
Donor negative, Recipient positive	10	18.5	12	18.5	
Donor negative, Recipient negative	34	63.0	42	64.6	
Missing	1	1.9	1	1.5	
Transplant era					
1996-1999	9	16.7	6	9.2	0.69
2000-2003	19	35.2	25	38.5	
2004-2007	17	31.5	22	33.8	
2008-2011	9	16.7	12	18.5	
T cell deplete					
Yes	43	79.6	54	83.1	0.41
No	4	7.4	2	3.1	
Missing	7	13.0	9	13.8	
Disease risk – EBMT score					
Good	19	35.2	32	49.2	0.20
Intermediate/Poor	34	63.0	33	50.8	
Missing	1	1.9	0	0.0	
Stem cell source					
BM	26	48.1	28	43.1	0.71
PBSC	28	51.9	37	56.9	
Previous autografts					
0	50	92.6	62	95.4	0.70
≥1	4	7.4	3	4.6	

CMV = Cytomegalovirus, BM = bone marrow, PBSC = peripheral blood stem cells.

Categorical variables were compared by Chi-squared test (or Fisher’s Exact test when n≤5 for any subgroup).

Continuous variables were compared by Mann-Whitney test. Statistically significant p-values are denoted in *italics*.

Table 2 – Univariate analyses of recipient and donor factors on OS, relapse, DFS and NRM

Variable	Valid cases (n)	5 year OS		5 year relapse [§]		5 year DFS [§]		1 year NRM [§]	
		%	P-value	%	P-value	%	P-value	%	P-value
Donor age, years									
<30	39	42.2	0.67	24.2	0.12	42.9	0.37	28.6	0.36
>30	80	37.2		39.2		32.6		20.2	
Recipient age, years									
<40	85	42.6	0.049	34.3	0.79	38.4	0.083	19.2	0.097
>40	34	28.5		35.3		29.1		32.4	
Donor sex									
Female	17	35.9	0.99	43.7	0.66	26.9	0.53	29.4	0.49
Male	102	38.8		33.1		37.3		21.9	
Recipient sex									
Female	46	39.0	0.97	37.9	0.47	32.5	0.59	19.8	0.51
Male	73	38.3		32.3		37.9		25.0	
Recipient-donor sex matching									
Matched	70	41.4	0.41	35.4	0.86	38.0	0.54	21.7	0.69
Mismatched	49	34.6		33.3		32.6		24.7	
Recipient-donor CMV matching									
Matched	91	40.8	0.17	32.8	0.33	38.2	0.14	21.1	0.52
Mismatched	26	29.4		43.5		25.4		26.9	
Transplant era									
1996-1999	15	60.0	0.45	28.6	0.049	50.0	0.60	21.4	0.11
2000-2003	44	34.1		50.0		31.8		13.6	
2004-2007	39	35.6		20.5		33.1		35.9	
2008-2011 [†]	21	38.6		31.2		40.7		19.9	
T cell deplete									
Yes	97	37.5	0.28	34.0	0.46	34.9	0.22	24.1	0.63
No	6	66.7		16.7		66.7		16.7	
Disease risk – EBMT score									
Good	51	36.7	0.89	26.7	0.12	31.2	0.72	28.0	0.30
Intermediate/Poor	67	39.3		40.8		38.1		19.6	
Stem cell source									
BM	54	46.0	0.13	37.7	0.59	39.5	0.49	18.9	0.41
PBSC	65	31.88		31.6		32.1		26.4	
Previous autografts									
0	112	40.1	0.028	34.0	0.62	37.2	0.063	21.7	0.18
≥1	7	14.3		42.9		14.3		42.9	
Donor KIR genotype									
KIR AA	35	48.9	0.060	38.7	0.60	46.5	0.087	8.7	0.019
KIR BX	84	34.4		32.8		31.3		28.9	
Donor Tel motif pattern									
Tel-AA	74	36.2	0.42	33.6	0.77	34.2	0.47	27.6	0.13
Tel-BX	45	42.3		36.1		38.2		15.6	
Donor Cen motif pattern									
Cen-AA	54	47.7	0.024	38.0	0.45	44.6	0.045	9.3	0.001
Cen-BX	65	31.2		31.5		28.6		34.4	
Cen-AA	54	47.7	0.010	38.0	0.75	44.6	0.031	9.3	0.005
Cen-AB	53	36.8		31.2		33.7		32.7	
Cen-BB	12	8.3		33.3		8.3		41.7	

[§] NRM/DFS/Relapse data missing for one transplant.

[†] Estimated incidence of OS, relapse and DFS at latest clinical follow-up (4 years) reported.

Statistically significant results (≤ 0.05) are italicized. OS = Overall survival, NRM = Non-relapse mortality, CMV = Cytomegalovirus, BM = bone marrow, PBSC = peripheral blood stem cells

Table 3 – Multivariate analysis of OS, NRM and death by infection

Variable	5 year OS		1 year NRM [†]		1 year death by infection [‡]	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Recipient age, years						
<40	1.00	-	1.00	-	1.00	-
>40	1.91 (1.15-3.16)	<i>0.012</i>	1.81 (0.82-4.01)	0.15	2.28 (0.91-5.69)	0.078
Transplant era						
1996-1999					1.00	-
2000-2003					1.15 (0.15-8.99)	0.89
2004-2007					5.27 (0.84-32.9)	0.075
2008-2011					0.74 (0.05-9.93)	0.82
Previous autografts						
0	1.00	-	1.00	-		
≥1	3.05 (1.30-7.15)	<i>0.010</i>	2.45 (0.55-10.92)	0.24		
Donor Cen motif pattern						
Cen-AA	1.00	-	1.00	-	1.00	-
Cen-BX	1.90 (1.17-3.10)	<i>0.010</i>	4.16 (1.58-11.00)	<i>0.004</i>	5.50 (1.49-20.32)	<i>0.011</i>

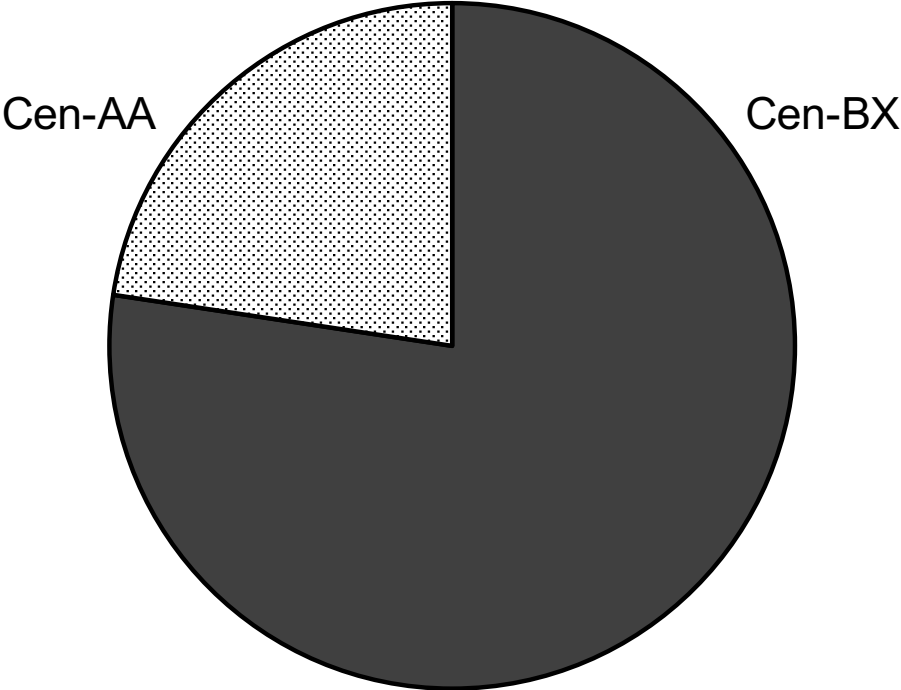
Statistically significant results (≤ 0.05) are italicized. OS = Overall survival, NRM = Non-relapse mortality

[†] NRM data missing for one transplant.

[‡] Cause-of-death data missing for three transplants.

Figure 1

KIR BX donors



Cen-AA donors

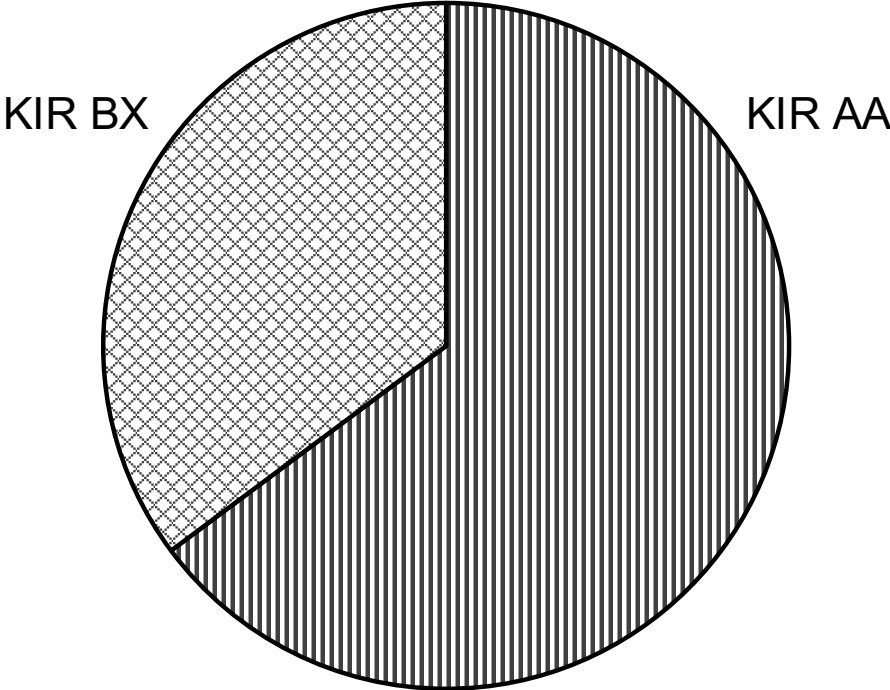


Figure 2

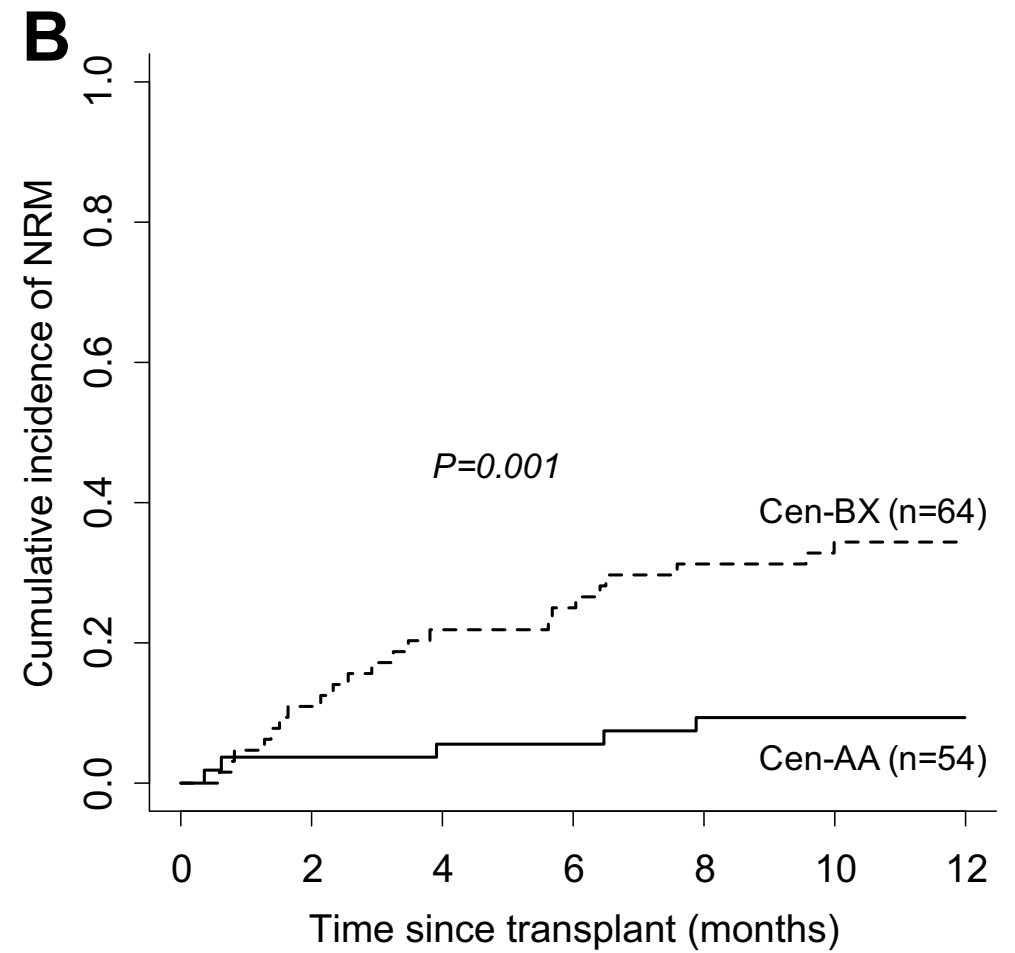
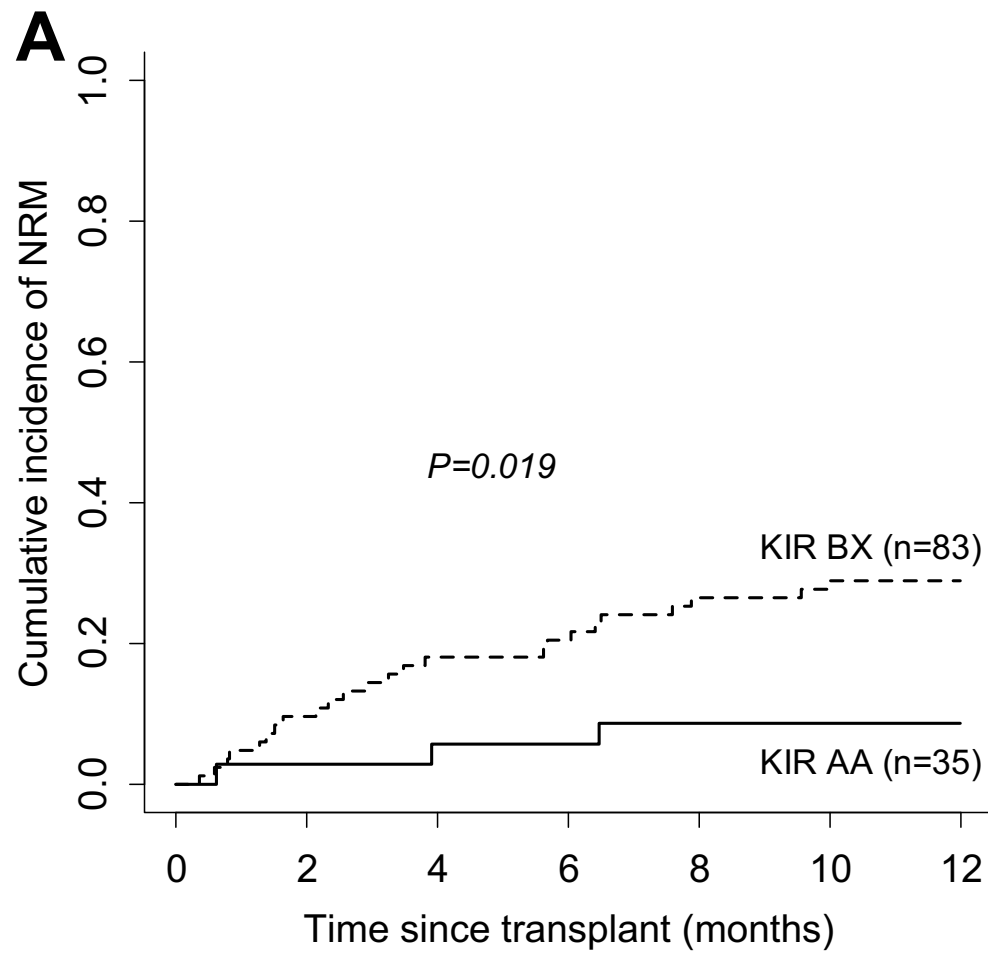


Figure 3

