A predictive classifier of poor prognosis in transplanted patients with juvenile myelomonocytic leukemia: a study on behalf of the Société Francophone de Greffe de Moelle et de Thérapie Cellulaire

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Supplemental Methods

Both bone marrow and peripheral stem cell donors underwent 4-digit molecular typing for HLA A, B, C, DR, and DQ subtypes, while cord blood (CB) had class 1 HLA typing (A and B subtypes) conducted via the serologic method, and class 2 (DR) typing performed using 4-digit molecular methods. Compatibility was defined as a 10 out of 10 HLA match for both matched sibling donors (MSD) and matched unrelated donors (MUD), and a 6 out of 6 matches for CB. Less than either 10 or 6 was classified as mismatched. Neutrophil engraftment was defined as absolute neutrophil count $\geq 0.5 \times 10^9$/L for 3 consecutive days and platelet engraftment as platelet count $\geq 50 \times 10^9$/L for 7 consecutive days, without transfusion. Graft failure was defined as either the absence of hematopoietic reconstitution of donor origin on day 60 (primary graft failure) or a loss of donor cells after transient donor engraftment (secondary graft failure)[7]. Full donor chimerism was defined as >95% of donor cells and mixed donor chimerism between 5 and 95%.

Supplemental Table 1: Conditioning regimen

Conditioning regimen	n
Busulfan-Fludarabine-Melphalan (Bu/Flu/Mel)	46
Busulfan-Cyclophosphamide-Melphalan (Bu/Cy/Mel)	41
Busulfan-Cyclophosphamide	17
Busulfan-Fludarabine-Thiothepa	9
TBI-Cyclophosphamide-Fludarabine	2
Busulfan-Cyclophosphamide-Clofarabine-Cytarabine	1
Busulfan-Fludarabine-Cyclophosphamide	1
Busulfan-Cyclophosphamide-Melphalan-Etoposide	1
TBI-Etoposide	1

TBI, total body irradiation. Busulfan was given orally (n=14, before October 2005) or intravenously (n=102, since November 2005)

Supplemental Table 2: Graft-versus-host disease prophylaxis according to donor.

	Identical sibling, n=24	Matched unrelated, n=46	Mismatched unrelated, n=45	Haploidentical, n=4
CSA	19	4	10	0
CSA/corticosteroids	0	8	19	0
CSA/MTX	4	31	6	1
CSA/MMF	0	2	7	1
CSA/MTX/sirolimus	0	0	1	0
CSA/MTX/tacrolimus	0	1	1	0
CSA/MMF/Cyclophosphamide	0	0	0	2
Missing	1	0	1	0

Supplemental Table 3: Patients characteristics of according to engraftment status

	Engraftment, n=100	No/lost engraftment, n=16
M/F ratio	2.3	1.6
Pre-HSCT treatment, no. (%)	n=99	
No or low-dose chemotherapy	73	14 (87.5)
AML-type chemotherapy	26	2 (12.5)
Splenectomy	2	3 (18.7)
RAS-pathway mutations, no. (%)	n=99	
PTPN11	42	4 (25.0)
KRAS	21	5 (31.2)
NRAS	19	3 (18.7)
CBL	4	3 (18.7)
NF1	6	1 (6.2)
Other	4	0
No mutation	3	0
Donor, no. (%)		
Match siblings	21	2 (12.5)
Haploidentical	3	1 (6.2)
Match unrelated	42	4 (25.0)
Mismatched unrelated	34	9 (56.2)
Source of cells, no. (%)		
Cord blood	29	8 (50.0)
Bone marrow	62	7 (43.7)
Peripheral blood	9	1 (6.2)
Conditioning, no. (%)		
Bu/Cy/Mel	37	2 (12.5)
Bu/Flu/Mel	42	3 (18.7)
Other	21	11 (68.7)

HSCT, hematopoietic stem cell transplant; AML, acute myeloid leukemia; HbF, fetal hemoglobin; Bu/Cy/Mel, busulfan/cyclophosphamide/melphalan; Bu/Flu/Mel, busulfan/fludarabine/melphalan;

Supplementary Table 4: Univariable predictive analyses of GVHD based on Fine & Gray models

Outcomes	Acute GVHD 2–4	Acute GVHD 3–4	Chronic GVHD
	100-day CI, 95%CI	100-day CI, 95%CI	36-month CI, 95%CI
Overall	53.8%, 44.4-62.3	31.9%, 23.7-40.4	36.0%, 27.2-44.9
Patient characteristics at diagnosis			
Age ≥ 2 years at diagnosis	1.14 (0.70-1.84)	1.02 (0.64-1.71)	0.86 (0.47-1.59)
Platelets ≥ 33 x10^9/L	0.82 (0.47-1.43)	0.57 (0.24-1.35)	0.93 (0.44-1.96)
Monocyte >7.2 x10^9/L	0.88 (0.49-1.56)	0.88 (0.47-1.63)	0.86 (0.41-1.80)
Myeloid precursors in PB	1.45 (0.50-4.16)	0.72 (0.25-2.03)	0.95 (0.38-2.39)
BM blasts ≥5%	1.36 (0.84-2.21)	1.39 (0.74-2.62)	1.13 (0.61-2.07)
Pre-HSCT BM ≥5%	1.45 (0.88-2.39)	1.16 (0.68-2.00)	1.19 (0.64-2.23)
Elevated HbF*	**0.52 (0.30-0.90)**	0.75 (0.37-1.51)	0.73 (0.35-1.52)
Abnormal karyotype	1.25 (0.76-2.05)	0.85 (0.44-1.63)	0.87 (0.47-1.62)
Monosomy 7	1.08 (0.62-1.89)	0.61 (0.25-1.46)	1.10 (0.54-2.24)
RAS-pathway mutations			
PTPN11	1.00	1.00	1.00
CBL	0.15 (0.02-1.24)	0.79 (0.13-4.75)	0.14 (0.02-1.13)
KRAS	0.65 (0.25-1.70)	0.75 (0.19-2.92)	**0.22 (0.07-0.64)**
NF1	0.82 (0.25-2.70)	1.10 (0.22-5.47)	**0.11 (0.01-0.91)**
NRAS	1.10 (0.43-2.82)	**3.44 (1.01-11.78)**	0.40 (0.14-1.13)
No/other	0.62 (0.25-1.52)	1.77 (0.54-5.88)	**0.38 (0.15-0.96)**
Additional alteration**	1.30 (0.78-2.16)	0.80 (0.42-1.51)	0.99 (0.52-1.87)
Pre-HSCT treatment			
No	1.00	1.00	1.00
Low-dose chemotherapy	0.90 (0.38-2.09)	0..71 (0.27-1.90)	1.37 (0.40-4.70)
AML-type chemotherapy	0.95 (0.38-2.35)	0.84 (0.29-2.44)	2.25 (0.62-8.13)
Transplant characteristics			
Female recipient sex	1.24 (0.75-2.05)	1.50 (0.80-2.84)	1.52 (0.82-2.82)
Female donor to male recipient	1.18 (0.63-2.20)	1.11 (0.51-2.44)	0.89 (0.45-1.75)
Age ≥ 2 years at HSCT	1.03 (0.63-1.68)	1.36 (0.70-2.65)	1.05 (0.56-1.97)
Time to HSCT ≥ 6 months	1.25 (0.76-2.04)	1.25 (0.66-2.35)	1.02 (0.55-1.87)
Donor			
Identical sibling	1.00	1.00	1.00
Matched unrelated	1.14 (0.56-2.29)	1.05 (0.42-2.66)	1.56 (0.60-4.07)
Mismatched relative	0.80 (0.22-2.95)	1.53 (0.40-5.91)	**3.24 (1.02-10.3)**
Mismatch unrelated	0.99 (0.48-2.02)	1.02 (0.40-2.56)	1.26 (0.47-3.39)
HLA disparities ≥ 2	0.69 (0.41-1.16)	0.81 (0.42-1.56)	0.87 (0.45-1.66)
Cord Blood source	0.63 (0.37-1.08)	0.65 (0.32-1.30)	0.62 (0.30-1.26)
Donor/recipient CMV status			
Negative/Negative	1.00	1.00	1.00
Negative/Positive	0.70 (0.31-1.58)	0.69 (0.26-1.84)	0.64 (0.24-1.69)
Positive/Negative	**1.64 (1.00-2.71)**	1.00 (0.43-2.18)	0.78 (0.32-1.90)
Positive/Positive	0.65 (0.29-1.45)	0.81 (0.33-2.00)	0.78 (0.31-1.98)
Conditioning			
Other	1.00	1.00	1.00
Bu/Cy/Mel	1.24 (0.65-2.36)	0.79 (0.33-1.90)	0.96 (0.46-2.03)
Bu/Flu/Mel	1.40 (0.76-2.58)	1.32 (0.62-2.78)	0.79 (0.37-1.70)
Anti-thymoglobulin	0.69 (0.42-1.12)	0.52 (0.27-1.02)	0.78 (0.42-1.45)

NA refers to the models that do not converge due to a low number of events in one stratum. Significant results are in bold letters.

* For patients ≥6 months,

** At least 1 alteration among the following genes: *ASXL1, JAK3, SETBP1,* or double RAS mutation or karyotype anomaly.
GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; BM, bone marrow; HbF, fetal hemoglobin; AML, acute myeloid leukemia; Bu/Cy/Mel, busulfan/cyclophosphamide/melphalan; Bu/Flu/Mel, busulfan/fludarabine/melphalan.

Supplementary Table 5: Univariable predictive analyses of the “stringent” EFS when additionally including beside relapses and deaths, secondary malignancies and secondary allografts as events

Outcomes		“Stringent” EFS
	No. of patients	60-month event-free survival, 95% CI
Overall	119	63.6%, 55.3-73.3
No. of events		46 events
Patient characteristics at diagnosis		
Age ≥ 2 years	55	**2.62 (1.42-4.82)**
Platelet ≥ 33 x10^9/L	28	0.93 (0.46-1.88)
Monocyte > Q3 (7.2 x10^9/L)	30	**1.92 (1.05-3.53)**
Myeloid precursors in PB	106	2.24 (0.54-9.26)
BM blasts ≥5%	49	0.98 (0.54-1.76)
Elevated HbF*	73/88	1.11 (0.53-2.31)
Abnormal karyotype		1.28 (0.71-2.32)
Monosomy 7	26	0.67 (0.31-1.44)
RAS-pathway mutations		
PTPN11	46	1.00
CBL	7	1.37 (0.27-6.78)
KRAS	26	0.56 (0.14-2.24)
NF1	8	2.14 (0.51-8.99)
NRAS	23	1.47 (0.40-5.34)
No/other	9	1.24 (0.37-4.18)
Additional mutations		
JAK3	10	1.67 (0.70-3.95)
SETBP1	9	1.93 (0.81-4.56)
ASXL1	11	0.90 (0.32-2.50)
Double RAS pathway mutation	25	1.22 (0.62-2.40)
Additional alteration**		
>=1 Alteration	67	1.59 (0.83-3.03)
>=2 Alterations	20	1.33 (0.66-2.68)
Pre-HSCT treatment		
Low-dose chemotherapy	77	1.00
No chemotherapy	13	0.30 (0.07-1.25)
AML-type chemotherapy	28	0.88 (0.45-1.75)
Transplant characteristics		
Male recipient sex	82	0.88 (0.48-1.64)
Female donor to male recipient	28	1.40 (0.73-2.68)
Age ≥ 2 years at HSCT	71	**2.28 (1.18-4.41)**
Pre-HSCT BM ≥5%	42	0.84 (0.45-1.55)
Time to HSCT ≥ 6 months	52	1.46 (0.82-2.61)
Donor		
Geno-Identical sibling	24	1.00
Matched unrelated	46	0.60 (0.27-1.32)
Mismatched relative	4	0.50 (0.06-3.89)
Mismatch unrelated	45	1.00 (0.48-2.09)
HLA disparities ≥ 2	40	1.11 (0.61-2.03)
Stem cells		
Bone marrow	70	1.00
Cord blood	39	1.07 (0.58-1.97)
Peripheral blood	10	0.48 (0.11-2.01)
Donor/recipient CMV status		
Negative/Negative	57	1.00

Negative/Positive	19	1.43 (0.64-3.19)
Positive/Negative	19	1.32 (0.55-3.16)
Positive/Positive	20	1.92 (0.86-4.29)
Conditioning		
Bu/Cy/Mel	41	1.00
Bu/Flu/Mel	46	0.87 (0.42-1.83)
Other	32	**2.04 (1.03-4.05)**
Anti-thymoglobulin	57	0.93 (0.52-1.66)

* For patients ≥6 months,
** At least 1 alteration among the following genes: *ASXL1, JAK3, SETBP1,* or double RAS mutation or karyotype anomaly.
NA refers to the models that do not converge due to a too low number of events in one stratum. Significant results are in bold letters.
EFS, event free survival; HSCT, hematopoietic stem cell transplantation; CB, cord blood; BM, bone-marrow; PB, peripheral blood; CMV, cytomegalovirus; Bu/Cy/Mel, busulfan/cyclophosphamide/melphalan; Bu/Flu/Mel, busulfan/fludarabine/melphalan.

Supplementary Table 6: Characteristics of patients at diagnosis according to monocyte count in peripheral blood

	AMC >7.2G/L n=30	AMC ≤7.2G/L n=89	*p-value*
M/F (ratio)	22/8 (2.75)	60/29 (2.1)	0.65
Age at diagnosis, median [IQR]	1.7 [0.7-3.1]	1.6 [0.8-3.3]	0.50
Peripheral blood cell count, median [IQR] x10^9/L			
White blood cells	59.2 [40.0-73.0]	21.6 [14-29.2]	<0.0001
Platelets <33 x10^9/L, n (%)	9/29 (31.0)	19/87 (21.8)	0.33
Platelets	53 [28-107]	60 [34-113]	0.82
Hemoglobin, g/dl	8.8 [7.2-10.1]	9.1 [8.1-10.4]	0.36
Neutrophils	17.7 [6.3-31.0]	6.9 [3.5-10.6]	0.0002
Eosinophils	0.7 [0-1.8]	0.27 [0.06-0.64]	0.22
Basophils	0.5 [0.3-0.9]	0.27 [0.06-0.41]	0.14
Lymphocytes	13.3 [9.1-19.4]	6.3 [4.7-10.1]	<0.0001
BM Blasts %, median [IQR]	5.2 [3.6-11.5]	3.5 [2.0-7.0]	0.008
Elevated HbF*, no. (%)	19/25 (76.0)	64/79 (81.0)	0.58
RAS-pathway mutations, no. (%)			
PTPN11	10 (33.3)	37 (41.6)	0.28
KRAS	5 (16.7)	21 (23.6)	
NRAS	6 (20)	17 (19.1)	
CBL	2 (6.7)	5 (5.6)	
NF1	5 (16.7)	3 (3.4)	
Other	0	4 (4.5)	
No mutation	1 (3.3)	2 (2.2)	
Abnormal karyotype, n (%)	12/29 (41.4)	33/84 (39.3)	1.00
Additional mutations, no. (%)			
JAK3	3/29 (10.3)	7/85 (8.2)	0.71
SETBP1	3/29 (10.3)	6/85 (7.1)	0.69
ASXL1	1/29 (3.4)	10/85 (11.7)	0.28
Double RAS pathway mutation	6/29 (20.7)	19/85 (22.3)	1.00
≥ 1 additional alteration, n (%)**	18/29 (62.1)	51/82 (62.2)	1.00
≥ 2 additional alterations, n (%)**	6/29 (20.7)	14/82 (17.0)	0.78

IQR, interquartile range; HbF, fetal hemoglobin; BM, Bone marrow.
* for patients ≥6 months; ** At least 1 or 2 alteration among the following genes: *ASXL1, JAK3, SETBP1,* or double RAS mutation or karyotype anomaly.

Supplementary Table 7: Patient characteristics and outcomes following HSCT in main studies published in JMML

Reference	HSCT period	N° of pts	RAS mut (%)	Time to HSCT (months)	PB/CB/BM (%)	HLA disparity ≥1 (%)	URD (%)	Conditioning (%)	Graft failure (%)	5-y EFS (%)	Risk factors for EFS	5-y OS (%)	Risk factors for OS	5-y TRM (%)	Risk factors for TRM	5-y RI (%)	Risk factors for RI
Smith et al, 2002	1990-1997	46	NA	8,7	NA	37	100	TBI-based (76), Bu-Cy (11), Bu-Cy-Mel (13)	4	24 (2y)	no	42 (2y)	no	18 (2y)	NA	58 (2y)	no
Manabe et al, 2002	1990-1997	27	NA	9	11/4/85	19	41	TBI-based (67), Bu-Cy-based (22), Others (11)	4	54 (4y)	NA	58 (4y)	**Abn karyotype**, age>1y	NA	NA	NA	NA
Locatelli et al, 2005	1993-2002	100	NA	6	14/7/79	NA	52	Bu-Cy-Mel (100)	5	52	age at dg≥4y, **age at HSCT ≥4y, female sex**	64	NA	13	female donor	35	**age at HSCT ≥4y,** female sex, age at dg≥4y, HbF≥40%, blast BM at HSCT≥20%.
Locatelli et al, 2013	1995-2010	110	NA	5,6	0/100/0	84	100	Bu-Cy-Mel (45), TBI-based (17), RIC (7), Others (41)	18	44	**Age at dg>1.4y, monosomy 7, HLA MM≥2**	52	**Age at dg >1.4y, monosomy 7,** AML-type chemotherapy	22	**monosomy 7,** female sex, no chemotherapy, **HSCT<2003**	33	**Age at dg >1.4y**
Stieglitz et al, 2015	2001-2006	44	NA	1.8	NA	NA	50	TBI-Cy (100)	4	39	NA	57	NA	7	NA	43	NA
Yabe et al, 2015	2001-2011	30	67	6	7/17/77	43	73	Bu-Flu-Mel (100)	20	53	HLA MM	72	NA	NA	NA	NA	NA
Dvorak et al, 2018	2013-2015	15	100	1.2 to 1.4	7/7/87	13	67	Bu-Cy-Mel (40), Bu-Flu (60)	7	47 (1.5y)	NA	64 (1.5y)	NA	NA	NA	NA	NA
Lin et al, 2019	2010-2018	47	94	4 to 4.4	91/0/9	60	26	Bu-Cy-based (43), Bu-Cy-VP16-based (53), Others (4)	4	55	Age at dg>2.6y	64	NA	11	NA	35	**HLA MM<2,** Age>2.6y, *PTPN11, KRAS, NRAS*
Yoshida et al, 2020	2000-2011	129	NA	6	8/23/69	48	66	Bu-Flu-Mel (46), Bu-Cy (23), other MAC (6), RIC (10), TBI-based (16)	12	46	Age at HSCT≥2y, Abn karyotype, **interval dg-HSCT>6 months, HSCT<2005, HLA MM≥2, CB**	64	Abn karyotype, **HSCT<2005, HLA MM≥2, TBI**	14	TBI	34	age at HSCT≥2y, **Abn karytype**, **CB,** HLA MM≥2
Eun Sang Yi et al, 2023	2000-2019	68	74	NA	61/22/16	54	65	Bu-Flu or Bu-Mel-based (43), Bu-Cy-based (48), TBI-based (9)	10	53	HbF≥40%, no *NRAS* mutation	62	NA	30	NA	26	**HbF≥40%, Abn karyotype, MSD**

In bold, variables significant in multivariate analysis

HSCT, hematopoietic stem cell transplantation; CB, cord blood; BM, bone-marrow; PB, peripheral blood; URD: unrelated donor; EFS, event free survival; OS, overall survival; TRM, treatment related mortality; RI, relapse incidence; NA, not available; TBI, total body irradiation; Bu, busulfan; Cy, cyclophosphamide; Mel, melphalan; Flu, fludarabine; RIC, reduced intensity conditioning; Dg, diagnostic; HLA MM, HLA mismatch; Abn, abnormal; HbF, fetal hemoglobin; MSD, matched sibling donor

Supplemental Figure legends

Supplemental figure 1: Pretransplant strategy according to the initiating RAS-mutation and effect of pre-HSCT treatment on BM blast percentage. (A) Time from JMML diagnosis to transplant (months, IQR) according to the initiating RAS mutation, n=118. (B) Pre-HSCT chemotherapy intensity according to the initiating RAS mutation, n=118. (C) BM blast (%) at JMML diagnosis (n=118) and prior to HSCT (n=88) according to the pre-HSCT chemotherapy received. Diagnostic BM blast count in patients with AML-type, low-dose, and no chemotherapy (10.8%, 4.5% and 4.2%, respectively). Pre-HSCT blasts count in patients with AML-type, low-dose, and no chemotherapy (4.3%, 5.7% and 2.8%, respectively). AML, acute myeloid leukemia; Dg, diagnostic; HSCT, hematopoietic stem cell transplant; BM, bone marrow.

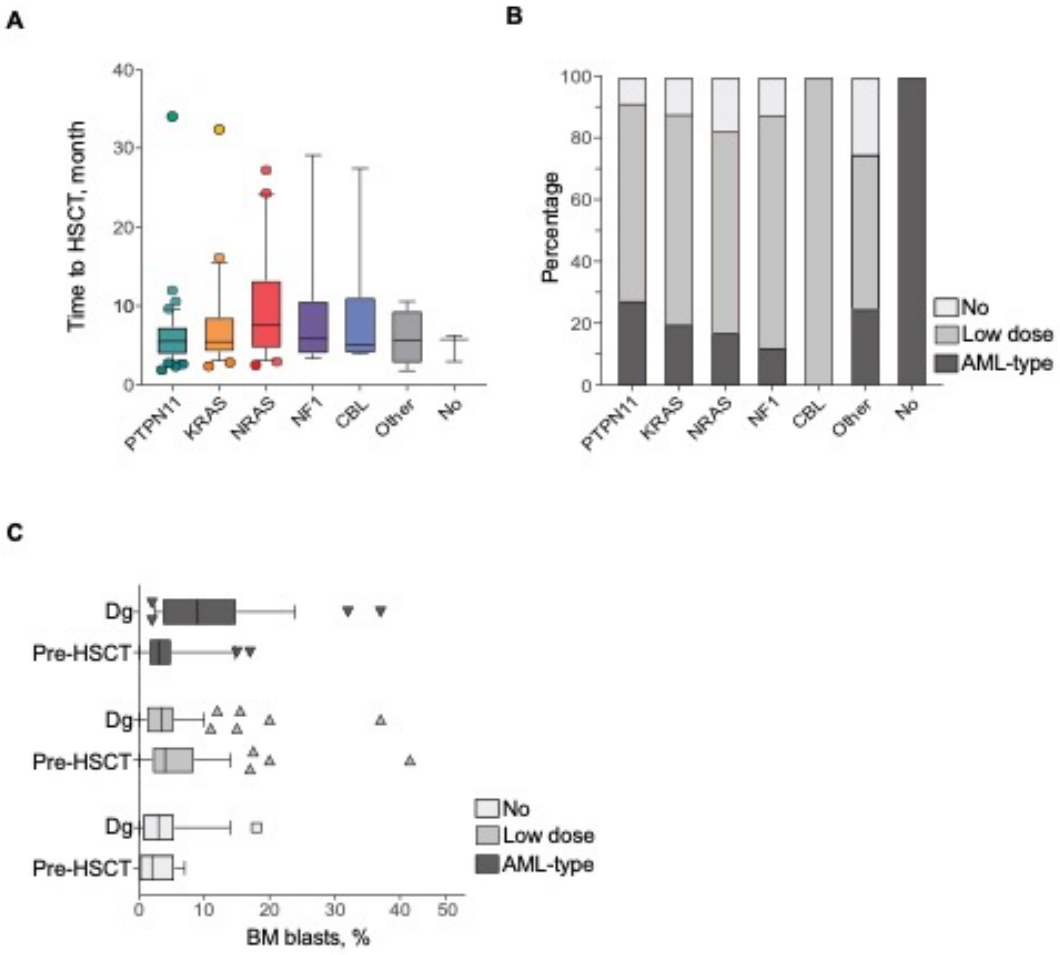
Supplemental figure 2: Outcome of the 16 patients who failed to engraft. HSCT, hematopoietic stem cell transplant; JMML, juvenile myelomonocytic leukemia.

Supplemental figure 2: GvHD and impact on JMML Relapse. Cumulative Incidence for grade 2-4 acute GvHD (A), and for chronic GvHD (B). Relapse-free survival according to the presence or absence of grade 2-4 acute GvHD (C) and Relapse-free survival according to the presence or absence of chronic GvHD (D) were analyzed using Kaplan-Meier methodology. CI, cumulative incidence; HSCT, hematopoietic stem cell transplant; RFS, relapse-free survival

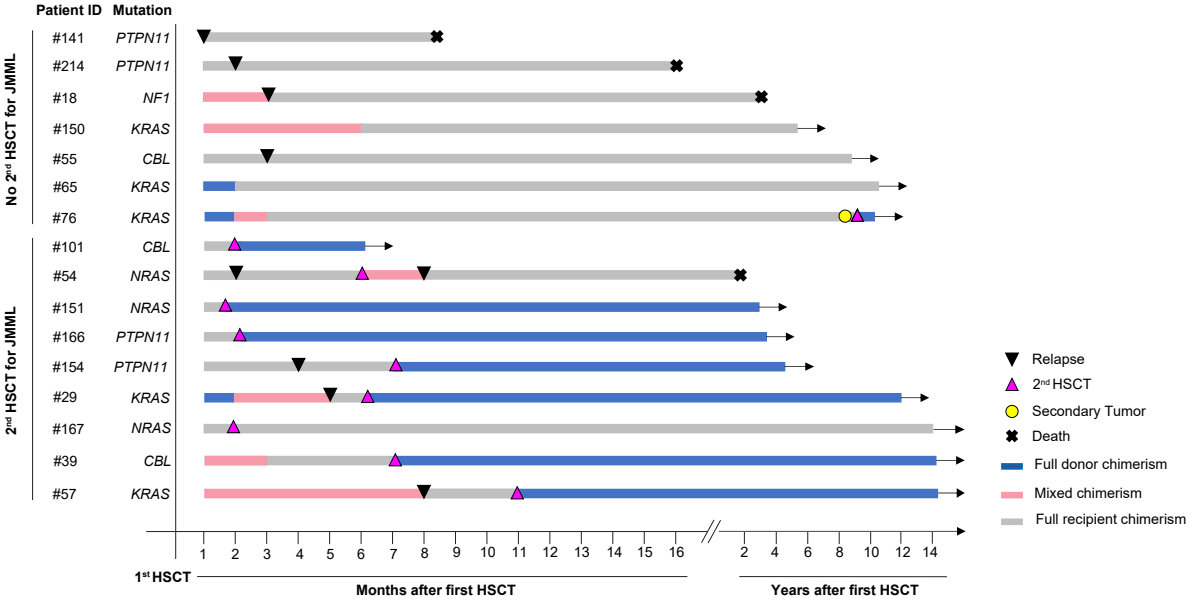
Supplemental figure 4: Stringent EFS probability. Stringent EFS was analyzed using

Kaplan-Meier methodology. Stringent EFS considers relapse, death, secondary allograft, and secondary malignancy as events. EFS, event-free survival; HSCT, hematopoietic stem cell transplant.

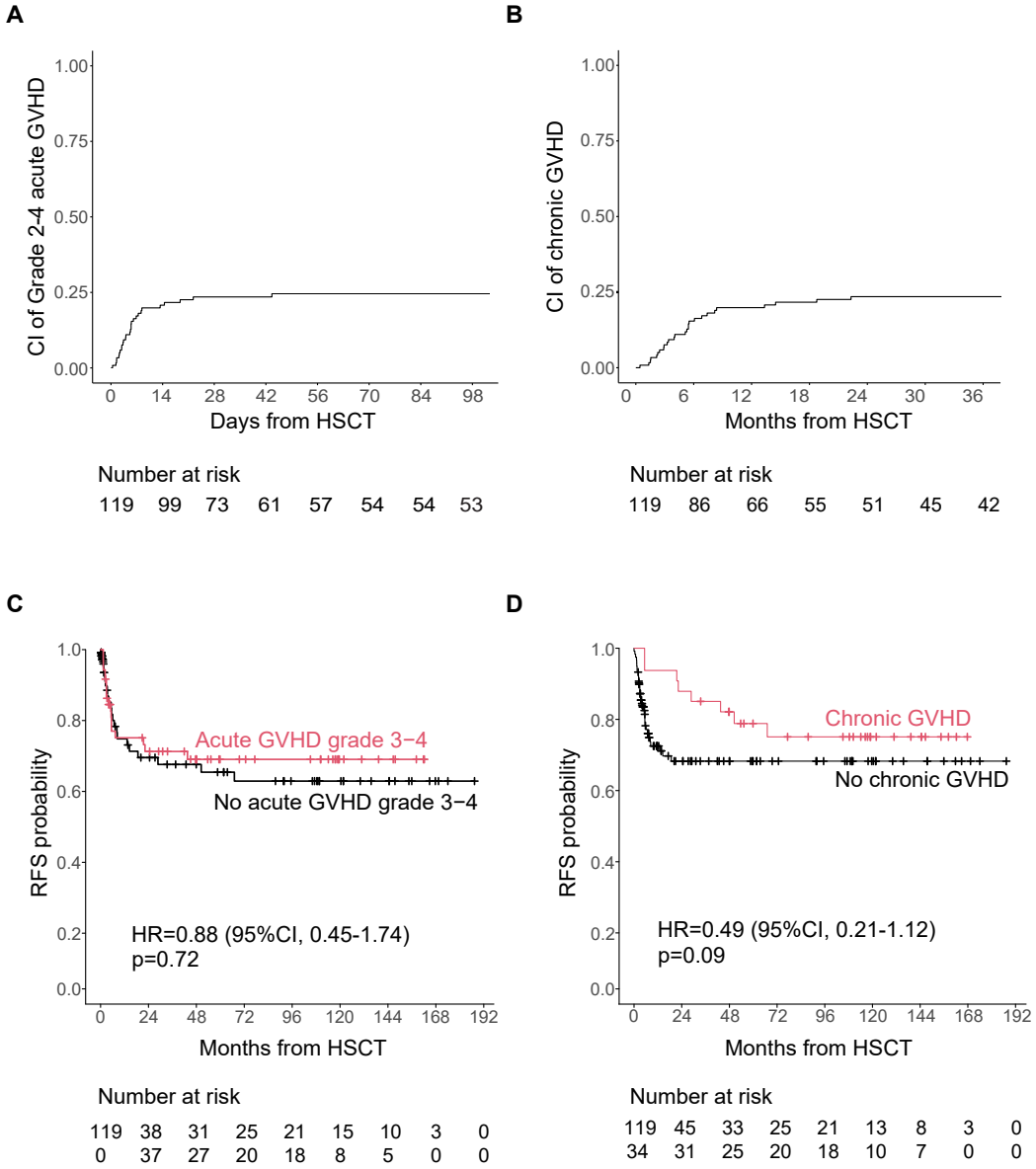
Supplemental Figure 1



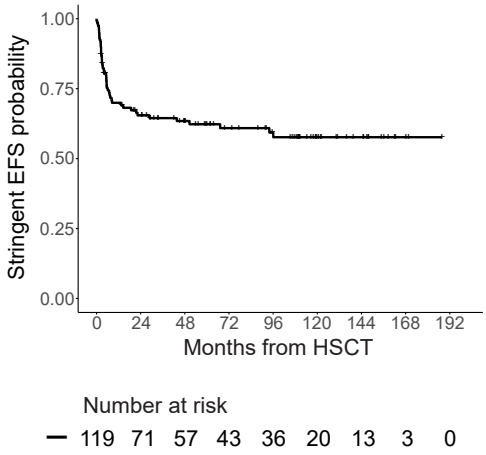
Supplemental Figure 2



Supplemental Figure 3



Supplemental Figure 4



Number at risk

—	119	71	57	43	36	20	13	3	0