TET2 mutation does not impact the prognosis of adult acute myeloid leukemia patients receiving a hematopoietic stem cell transplantation in first remission: similar outcome following matched sibling and unrelated *versus* haploidentical donor transplants in a multi-center retrospective analysis from the Global Committee and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

The Ten-Eleven Translocation (*TET*) 2 gene, a member of the TET family of enzymes, is located on chromosome 4q24, and its protein product TET2 modulates DNA hydroxymethylation to promote DNA demethylation with significant implications in hematopoiesis and cancer.[1] Some reports have shown that *TET2* mutation is related to poorer outcomes in AML patients,[2,3] while others have shown no correlation with prognosis.[4] Allogeneic hematopoietic stem cell transplantation (HSCT) is one of the most effective therapies for hematologic malignancies. However, the effect of *TET2* mutations for acute myeloid leukemia (AML) patients after transplantation remains controversial and data are very limited. Our international multicenter retrospective study aimed to evaluate the impact of *TET2* mutations on AML patients undergoing transplantation in first CR (CR1) and to explore their potential association with different stem cell sources, including haploidentical donors (Haplo), matched sibling donors (MSD), and 10/10 or 9/10 unrelated donors (UD).

This multi-center retrospective study utilized the European Society for Blood and Marrow Transplantation (EBMT) registry dataset and was approved by the scientific board of the Acute Leukemia Working Party of the EBMT. Our first objective was to compare the outcomes of patients with and without *TET2* mutation. Since the reporting of *TET2* mutation was not mandatory in the EBMT registry during the period covered by this study, we were concerned by a possible bias with over-reporting of the presence of a mutation as compared to its absence. To ensure exhaustivity of information, we initiated an additional specific data collection to enable a valid comparison of outcomes. The second objective was to evaluate the impact of donor types on outcomes of patients with *TET2* positive mutation: all patients with a positive *TET2* mutation recorded initially in the registry and/or the specific data base were included.

The data base used to compare the outcome of *TET2* mutated *versus* unmutated AML patients consisted of 755 AML patients, all tested for *TET2*, with 632 *TET2* unmutated and 123 *TET2* mutated AML. *Online Supplementary Table S1* shows the characteristics of the two patient populations, *TET2* unmutated and mutated. The two populations exhibited comparable molecular profiles across most markers analyzed (*FLT3-ITD, DNMT3A, CEBPA, RUNX1, TP53, BCOR, STAG2, U2AF1, ZSZR2*), with notable exceptions observed in *NPM1, SRSF2, ASXL1*, and *EZH2* mutations that showed higher prevalence in *TET2*-mutated AML, while *SF3B1* mutations showed a lower prevalence in *TET2*-mutated AML.

Pair-matching was carried out for patient age, sex, year of transplant, and donor origin. We were able to pair-match 116 AML patients bearing a *TET2* mutation with 320 patients with no *TET2* mutation. Table 1 and *Online Supplementary Table S2* show the characteristics of the two pair-matched populations, *TET2* unmutated and mutated.

There was no difference in post-transplant outcomes in pair-matched AML patients with or without a *TET2* mutation (Figure 1). At the 2-year follow-up, overall survival (OS) rates reached 72% (95% confidence interval [CI]: 66.1-77.1%) *versus* 68.2% (95% CI: 57.7-76.6%) (hazard ratio [HR] 1.02, 95% CI: 0.67-1.55; *P*=0.92), with leukemia-free survival (LFS) at 59.5% (95% CI: 53.3-65.1%) *versus* 59.2% (95% CI: 48.4-68.5%) (HR 0.92, 95% CI: 0.64-1.32; *P*=0.64). Relapse incidence (RI) measured 25.3% (95% CI: 20.2-30.7%) *versus* 21.8% (95% CI: 14-30.7%) (HR 0.79, 95% CI: 0.48-1.31; *P*=0.36), while non-relapse mortality (NRM) was 15.2% (95% CI: 11.4-19.6%) *versus* 19.1% (95% CI: 11.9-27.6%) (HR 1.11, 95% CI: 0.67-1.84; *P*=0.7). Graft-*versus*-host disease-free, relapse-free survival (GRFS) remained comparable at 50% (95% CI: 43.8-56%) *versus* 48.4% (95% CI: 37.8-58.2%) (HR 0.93, 95% CI: 0.67-1.28; *P*=0.64). The 100-day cumulative incidence of grade II-IV acute graft-*versus*-host disease (GvHD) was 22.8% (95% CI: 18.3-27.6%) *versus* 18% (95% CI: 11.5-25.7%) (HR 0.80, 95% CI: 0.48-1.33; *P*=0.39), with grade III-IV at 6.8% (95% CI: 4.4-10%) *versus* 4.5% (95% CI: 1.7-9.6%) (HR 0.78, 95% CI: 0.30-2.02; *P*=0.61).

Table 1. Characteristics of the two pair-matched groups *TET2* unmutated and mutated.

Variables	Modalities	N=436	Neg, N=320	Pos, N=116	*P*
Year of HSCT	Median [IQR] (range)	2019 [2018-2021] (2015-2022)	2019 [2018-2021] (2015-2022)	2019 [2018-2021] (2015-2022)	0.94
Age in years at HSCT	Median [IQR] (range)	58.0 [49.4-64] (18.5-75)	57.6 [49.7-63.8] (18.5-75)	58.7 [46.7-65] (21.2-74.9)	0.48
Sex	Female, N (%) Male, N (%)	214 (49.1) 222 (50.9)	160 (50) 160 (50)	54 (46.6) 62 (53.4)	0.52
Karnofsky score	<90, N (%) >90, N (%) Missing, N	88 (21.3) 326 (78.7) 22	60 (19.5) 248 (80.5) 12	28 (26.4) 78 (73.6) 10	0.13
AML type	*De novo*, N (%) SecAML, N (%) Missing, N	373 (85.9) 61 (14.1) 2	278 (87.1) 41 (12.9) 1	95 (82.6) 20 (17.4) 1	0.23
MRD	Negative, N (%) Positive, N (%) Missing, N	150 (62.2) 91 (37.8) 195	103 (56.6) 79 (43.4) 138	47 (79.7) 12 (20.3) 57	0.002
N of *TET2* mutations	1, N (%) 2, N (%) 3, N (%) 4, N (%)	-	-	93 (80.2) 17 (14.7) 4 (3.4) 2 (1.7)	Not done
TET2 max VAF	Median [IQR] (range) Missing, N	-	-	48 [42-51] (1-100) 25	Not done
ELN2022 cytogenetics	Favorable, N (%) Intermediate, N (%) Adverse, N (%) Missing, N	18 (4.5) 276 (69.3) 104 (26.1) 38	14 (4.7) 198 (66.9) 84 (28.4) 24	4 (3.9) 78 (76.5) 20 (19.6) 14	0.2
Cell source	PB, N (%) BM, N (%) CB, N (%)	419 (96.1) 15 (3.4) 2 (0.5)	311 (97.2) 8 (2.5) 1 (0.3)	108 (93.1) 7 (6) 1 (0.9)	0.12
Donor type	MSD, N (%) Matched other relative, N (%) Syngeneic, N (%) Haplo, N (%) MMR (missing HLA), N (%) MMR 1 locus, N (%) UD 10/10, N (%) UD 9/10, N (%) UD <=8/10, N (%) UD (missing HLA), N (%) UCB (missing HLA), N (%)	125 (28.7) 11 (2.5) 1 (0.2) 92 (21.1) 2 (0.5) 3 (0.7) 154 (35.3) 25 (5.7) 2 (0.5) 19 (4.4) 2 (0.5)	92 (28.7) 10 (3.1) 0 (0) 64 (20) 2 (0.6) 2 (0.6) 117 (36.6) 15 (4.7) 1 (0.3) 16 (5) 1 (0.3)	33 (28.4) 1 (0.9) 1 (0.9) 28 (24.1) 0 (0) 1 (0.9) 37 (31.9) 10 (8.6) 1 (0.9) 3 (2.6) 1 (0.9)	-
Female to male	No, N (%) Yes, N (%)	371 (85.1) 65 (14.9)	270 (84.4) 50 (15.6)	101 (87.1) 15 (12.9)	0.49
CMV donor to patient	Neg to Neg, N (%) Neg to Pos, N (%) Pos to Neg, N (%) Pos to Pos, N (%) Missing, N	69 (16.4) 102 (24.3) 38 (9) 211 (50.2) 16	52 (16.5) 78 (24.8) 34 (10.8) 151 (47.9) 5	17 (16.2) 24 (22.9) 4 (3.8) 60 (57.1) 11	0.13
Myeloablativity	No, N (%) Yes, N (%) Missing, N	241 (56.8) 183 (43.2) 12	179 (56.5) 138 (43.5) 3	62 (57.9) 45 (42.1) 9	0.79
In vivo TCD	No, N (%) Yes, N (%) Missing, N	192 (44.2) 242 (55.8) 2	141 (44.1) 179 (55.9) 0	51 (44.7) 63 (55.3) 2	0.9
Use of PTCy	No, N (%) Yes, N (%) Missing, N	275 (63.4) 159 (36.6) 2	205 (64.1) 115 (35.9) 0	70 (61.4) 44 (38.6) 2	0.61

AML: acute myeloid leukemia; BM: bone marrow; CB: cord blood; CMV: cytomegalovirus; HSCT: hematopoietic stem cell transplantation; IQR: interquartile range; MMR: mismatched related; MRD: measurable residual disease; MSD: matched sibling donor; N: number; Neg: negative; PB: peripheral blood; Pos: positive; PTCy: post-transplant cyclophosphamide; SecAML: secondary AML; TCD: T-cell depletion; UCB: umbilical cord blood; UD: unrelated donor.

The 2-year cumulative incidence of chronic GvHD was 32% (95% CI: 26.4-37.8%) *versus* 25.9% (95% CI: 17.5-35.1%) (HR 0.80, 95% CI: 0.52-1.22; *P*=0.3), including extensive chronic GvHD at 9.4% (95% CI: 6.1-13.4%) *versus* 10.9% (95% CI: 5.5-18.3%) (HR 1.04, 95% CI: 0.55-2.00; *P*=0.9).

A first important finding of this study concerns the prognostic impact of the *TET2* mutation: we observed in our series that *TET2* mutation was not a poor prognostic factor in AML patients transplanted in CR1. In contrast to previous studies suggesting an unfavorable prognostic impact of TET2 mutations,[5,6] our present study, through pair-matched analysis of a total population of 436 patients, demonstrated no significant difference in transplantation outcomes between patients with or without *TET2* mutations. These findings align with recent retrospective registry studies reporting similar results in non-high-risk AML.[7,8]

Interestingly, the association between *TET2* variant allele frequency (VAF) and patient prognosis is attracting growing attention. Data from elderly patients in the PETHEMA-FLU-GAZA phase III clinical trial demonstrated that an increase in *TET2* VAF was associated with a higher overall response rate.[9] Another study has shown that *TET2* VAF was inversely associated with both survival and the presence of adverse cytogenetic abnormalities.[10] *TET2* mutations have been reported to be associated with clonal hematopoiesis (CH), a condition prevalent in healthy aging individuals, and linked to an increased risk of leukemia.[11] The potential correlations among *TET2*, CH, and transplant outcomes warrant further investigation. Available VAF data of *TET2* are shown in Table 1. However, further analysis could not be conducted on the prognostic value of VAF due to significant data missing.

The registry contained data from 644 adult AML patients with *TET2* mutations receiving a first HSCT in 127 centers of EBMT from January 2013 and December 2022 (*Online Supplementary Table S3*).

In multivariable analysis (Table 2), RI was significantly high-

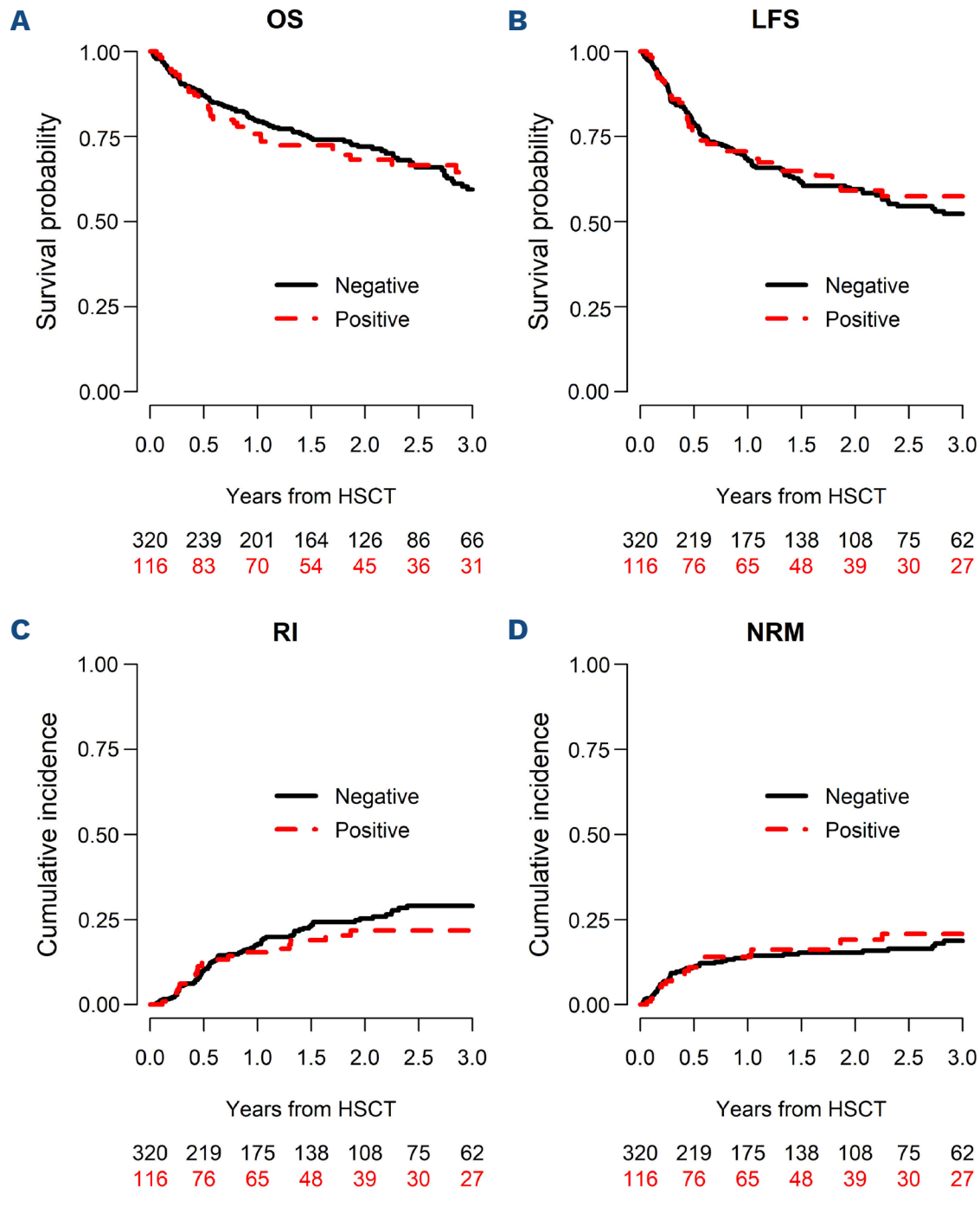

Figure 1. Transplant outcomes of adult acute myeloid leukemia patients with and without a *TET2* mutation following a hematopoietic stem cell transplantation in first remission. (A) Overall survival (OS). (B) Leukemia-free survival (LFS). (C) Relapse incidence (RI). (D) Non-relapse mortality (NRM). HSCT: hematopoietic stem cell transplantation.

Table 2. Multivariable analysis of factors affecting transplant outcomes in acute myeloid leukemia patients with a *TET2* mutation.

Variables	LFS *P*, HR (95% CI)	OS *P*, HR (95% CI)	RI *P*, HR (95% CI)	NRM *P*, HR (95% CI)	Grade II-IV acute GvHD *P*, HR (95% CI)
Donor type					
MSD	1	1	1	1	1
UD 10/10	0.84, 1.04 (0.69-1.57)	0.96, 1.01 (0.65-1.58)	0.56, 1.16 (0.70-1.94)	0.71, 0.89 (0.46-1.69)	0.08, 1.54 (0.95-2.50)
Haplo	0.87, 1.04 (0.64-1.70)	0.79, 1.07 (0.64-1.80)	0.92, 1.03 (0.55-1.92)	0.95, 0.98 (0.46-2.09)	0.07, 1.64 (0.96-2.80)
UD 9/10	0.003, 2.20 (1.31-3.70)	0.003, 2.29 (1.33-3.96)	0.01, 2.33 (1.21-4.48)	0.09, 2.04 (0.90-4.59)	0.78, 0.89 (0.40-2.01)
Cytogenetic AML classification					
Good/ Interm /Failed/NA *vs.* Poor	0.06, 1.44 (0.99-2.09)	0.14, 1.35 (0.91-2.01)	0.006, 1.85 (1.19-2.86)	0.55, 0.80 (0.40-1.63)	0.01, 1.74 (1.14-2.64)
Type of AML					
De novo *vs.* secAML	0.03, 1.49 (1.03-2.15)	0.007, 1.68 (1.15-2.45)	0.17, 1.39 (0.87-2.22)	0.07, 1.70 (0.96-2.99)	0.56, 1.15 (0.73-1.81)
Myeloablative regimen					
No *vs.* Yes	0.47, 1.14 (0.80-1.62)	0.18, 1.29 (0.89-1.85)	0.69, 1.09 (0.71-1.69)	0.66, 1.13 (0.66-1.94)	0.03, 0.64 (0.43-0.96)
Female to Male					
No *vs.* Yes	0.30, 1.24 (0.83-1.86)	0.28, 1.26 (0.83-1.91)	0.53, 1.18 (0.71-1.96)	0.53, 1.23 (0.65-2.32)	0.90, 0.97 (0.59-1.59)
Patient CMV					
Negative *vs.* Positive	0.10, 0.76 (0.55-1.05)	0.66, 0.92 (0.65-1.31)	0.42, 0.85 (0.56-1.27)	0.18, 0.70 (0.42-1.17)	0.34, 1.21 (0.82-1.76)
Year (effect for 2 y)	0.32, 1.10 (0.91-1.34)	0.44, 1.09 (0.88-1.34)	0.06, 1.27 (0.99-1.62)	0.32, 0.86 (0.65-1.15)	0.005, 0.76 (0.63-0.92)
Age (effect for 10 y)	<0.001, 1.36 (1.14-1.62)	<0.001, 1.60 (1.31-1.96)	0.04, 1.24 (1.01-1.53)	<0.001, 1.66 (1.23-2.24)	0.53, 1.06 (0.88-1.28)
Months between diagnosis and HSCT	0.93, 1.00 (0.97-1.02)	0.90, 1.00 (0.98-1.02)	0.82, 1.00 (0.97-1.03)	0.96, 1.00 (0.96-1.04)	0.39, 0.98 (0.93-1.03)

Variables	Grade III-IV acute GvHD *P*, HR (95% CI)	Chronic GvHD *P*, HR (95% CI)	Extensive chronic GvHD *P*, HR (95% CI)	GRFS *P*, HR (95% CI)
Donor type				
MSD	1	1	1	1
UD 10/10	0.44, 0.72 (0.31-1.67)	0.27, 0.78 (0.50-1.22)	0.27, 0.70 (0.37-1.32)	0.67, 0.93 (0.67-1.30)
Haplo	0.67, 0.81 (0.30-2.15)	0.61, 0.88 (0.53-1.45)	0.39, 0.72 (0.34-1.54)	0.31, 0.81 (0.55-1.21)
UD 9/10	0.74, 1.22 (0.38-3.92)	0.19, 0.61 (0.29-1.28)	0.36, 0.60 (0.19-1.82)	0.13, 1.43 (0.90-2.27)
Cytogenetic AML classification				
Good/Interm/Failed/NA *vs.* Poor	0.17, 1.71 (0.79-3.72)	0.56, 0.87 (0.54-1.41)	0.59, 0.81 (0.38-1.73)	0.23, 1.22 (0.88-1.70)
Type of AML				
De novo vs. secondary AML	0.34, 1.51 (0.64-3.56)	0.82, 1.06 (0.65-1.73)	0.97, 1.02 (0.5-2.04)	0.15, 1.27 (0.92-1.77)
Myeloablative regimen				
No *vs.* Yes	0.33, 0.68 (0.31-1.49)	0.85, 1.04 (0.68-1.58)	0.43, 0.77 (0.41-1.47)	0.82, 0.97 (0.73-1.29)
Female to Male				
No *vs.* Yes	0.17, 1.76 (0.79-3.93)	0.99, 1.00 (0.63-1.57)	0.90, 0.96 (0.47-1.95)	0.32, 1.19 (0.84-1.67)
Patient CMV				
Negative *vs.* Positive	0.09, 1.97 (0.90-4.31)	0.91, 1.02 (0.69-1.53)	0.84, 0.94 (0.52-1.69)	0.68, 0.94 (0.72-1.24)
Year (effect for 2 y)	0.10, 0.74 (0.51-1.07)	< 0.001, 0.67 (0.54-0.83)	0.049, 0.72 (0.52-0.99)	0.39, 0.93 (0.80-1.09)
Age in y (effect for 10 y)	0.12, 0.77 (0.56-1.07)	0.42, 1.07 (0.91-1.27)	0.04, 1.34 (1.02-1.77)	0.004, 1.23 (1.07-1.41)
Months between diagnosis and HSCT	0.18, 0.87 (0.71-1.07)	0.81, 1.00 (0.97-1.03)	0.15, 1.02 (0.99-1.05)	0.66, 1.00 (0.98-1.02)

95% CI: 95% confidence interval; AML: acute myeloid leukemia; CMV: cytomegalovirus; GRFS: graft-*versus*-host disease-free, relapse-free survival; GvHD: graft-*versus*-host disease; Haplo: haploidentical donor; HR: hazard ratio; HSCT: hematopoietic stem cell transplantation; Interm: intermediate; LFS: leukemia-free survival; MSD: matched sibling donor; NA: not available; NRM: non-relapse mortality; OS: overall survival; RI: relapse incidence; secAML: secondary AML; UD: unrelated donor; y: years.

er in 9/10 UD (HR=2.33, 95% CI: 1.21-4.48; *P*=0.01), and LFS (HR=2.20, 95% CI: 1.31-3.70; *P*<0.01) and OS (HR=2.29, 95% CI: 1.33-3.96; *P*<0.01), significantly lower as compared to MSD as reference. There were no significant differences for UD10/10 and Haplo compared to MSD. There were no significant differences among the donor groups regarding GvHD outcomes and GRFS.

The poor-cytogenetic risk group had a higher RI (HR=1.85, 95% CI: 1.19-2.86; *P*<0.01), and a higher incidence of grade II-IV acute GvHD (HR=1.74, 95% CI: 1.14-2.64; *P*=0.01) as compared to other groups combined as reference. Secondary AML had LFS (HR=1.49, 95% CI: 1.03-2.15; *P*<0.05) and OS (HR=1.68, 95% CI: 1.15-2.45; *P*<0.01) significantly reduced as compared to *de novo* AML.

Increasing patients' age by 10-year increments negatively influenced outcome, with higher RI (HR=1.24, 95% CI: 1.01-1.53; *P*=0.04), more extensive chronic GvHD (HR=1.34, 95% CI: 1.02-1.77; *P*=0.04), higher NRM (HR=1.66, 95% CI: 1.23-2.24; *P*<0.01), lower LFS (HR=1.36, 95% CI: 1.14-1.62; *P*<0.01), OS (HR=1.60, 95% CI: 1.31-1.96; *P*<0.01), and GRFS (HR=1.23, 95% CI: 1.07-1.41; *P*<0.01). Female donor to male recipient, patient CMV status, and interval between diagnosis and HSCT did not independently affect the transplant outcomes.

Outcomes improved over time. A later year of transplantation (by 2-year increments) was associated with a decrease in the incidences of stage II-IV acute GvHD (HR=0.76, 95% CI: 0.63-0.92; *P*<0.01), chronic GvHD (HR=0.67, 95% CI: 0.54-0.83; *P*<0.01), and extensive chronic GvHD (HR=0.72, 95% CI: 0.52-0.99; *P*<0.05). *Online Supplementary Figure S1* shows the outcomes post transplant of AML patients with a *TET2* mutation for the four stem cell donor groups.

A second finding is that there was no difference in the outcomes observed when considering MSD, Haplo or 10/10 unrelated donors for AML patients with a *TET2* mutation. Only the use of a 9/10 UD was significantly associated with a higher RI and a lower LFS and OS. Similar findings have already been reported by the EBMT in other AML categories of patients classified as high-risk, such as AML patients with *KMT2A* rearrangements[12] or core-binding factor mutated patients transplanted in second complete remission.[13] Previous research had indicated that HLA mismatch may amplify T-cell alloreactivity, which in turn could enhance the graft-*versus*-leukemia effect, thereby potentially reducing the chances of disease relapse.[14] However, relapse is influenced by various factors, such as genetic and molecular abnormalities, pre-transplant residual disease, and others. In our study, the 9/10 UD group was associated with a higher proportion of secondary AML (21.6%) and AML classified as cytogenetic adverse (20.4%) compared to other groups. Therefore, the poorer risk profile may have contributed to the higher relapse rate observed in the 9/10 UD group.

High-risk AML patients are associated with a higher incidence of grade II-IV acute GvHD, which may be attributed to the use of more intensive conditioning regimens, such as high-dose radiation or chemotherapy, to control disease progression. These aggressive conditioning approaches lead to significant tissue damage and cytokine release, thereby promoting donor T-cell activation and triggering GvHD. Besides, the decrease in the incidence of acute and chronic GvHD over time has most likely been the result of recent improvements in GvHD prophylaxis, such as post-transplant cyclophosphamide, improvement in the diagnosis and management of GvHD, and better control of viral infections.

Results from our study show that *TET2* mutation has no impact on the prognosis of patients transplanted in CR1 and all donors, including haploidentical donors, can be used for transplanting AML patients with *TET2* mutations. Haplo transplantation expands the choice of donors, and more and more transplant donors are family members than ever before. The scope of Haplo has enlarged since Haplo means not only first but also second degree family members, both of which are safe and effective for transplantation.[15]

In conclusion, *TET2* mutation is not a poor prognostic factor in AML patients transplanted in CR1. AML patients with *TET2* mutations showed no different outcomes following MSD, haplo, or 10/10 UD allo-HSCT, while 9/10 UD was associated with worse relapse and survival. Poor outcomes were also linked to older age, secondary AML, and adverse cytogenetics.

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No conflicts of interest to disclose.

Contributions

LL was a principal investigator and wrote the first draft of the manuscript. YY was a principal investigator. J-EG performed the statistical analysis. NCG Sr. supervised the study. All authors reviewed the manuscript and contributed to its revision.

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Data-sharing statement

Data available on request from the authors.

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