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Mohty, R.; Bazarbachi, A.H.; Labopin, M.; Esteve, J.; Kröger, N.; Cornelissen, J.J.; ... ; Mohty, M.

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Isocitrate dehydrogenase (IDH) 1 and 2 mutations predict better outcome in patients with acute myeloid leukemia undergoing allogeneic hematopoietic cell transplantation: a study of the ALWP of the EBMT

Razan Mohty[1,2✉], Abdul Hamid Bazarbachi[2,3], Myriam Labopin[2,4,5], Jordi Esteve[6], Nicolaus Kröger[7], Jan J. Cornelissen[8], Didier Blaise[9], Gerard Socié[10], Sébastien Maury[11], Arnold Ganser[12], Tobias Gedde-Dahl[13], Peter von dem Borne[14], Jean Henri Bourhis[15], Claude Eric Bulabois[16], Ibrahim Yakoub-Agha[17], Caroline Pabst[18], Stéphanie Nguyen[19], Patrice Chevallier[20], Anne Huynh[21], Ali Bazarbachi[22], Arnon Nagler[23], Fabio Ciceri[24] and Mohamad Mohty[2,4,5]

Isocitrate dehydrogenase 1 and 2 (*IDH1* and *IDH2*) mutations have uncertain prognostic implications in AML. We investigate the impact *IDH1* and *IDH2* mutations in AML patients undergoing allogeneic hematopoietic cell transplantation (allo-HCT) in first complete remission (CR1). In total, 1515 adult patients were included, 15.91% ($n = 241$) carried *IDH1* mutation (m*IDH1*), and 26.27% ($n = 398$) *IDH2* mutation (m*IDH2*) and 57.82% ($n = 876$) had no-IDH mutation. *NPM1* was frequently encountered with *IDH1* mutation (no-IDH group, $n = 217$, 24.8%, m*IDH1*, $n = 103$, 42.7%, m*IDH2*, $n = 111$, 27.9%, $p < 0.0001$). At day 180, the cumulative incidence (CI) of grade II-IV acute graft-versus-host disease (GVHD) was significantly lower in m*IDH1* and m*IDH2* compared to no-IDH groups (Hazard ratio [HR] = 0.66 (95% CI 0.47–0.91), $p = 0.011$; HR = 0.73 (95% CI 0.56–0.96), $p = 0.025$, respectively). In the m*IDH1* group, overall survival (OS) was improved compared to no-IDH (HR = 0.68 (95% CI 0.48–0.94), $p = 0.021$), whereas m*IDH2* was associated with lower incidence of relapse (HR = 0.49 (95% CI 0.34–0.7), $p < 0.001$), improved leukemia free survival (LFS) (HR = 0.7 (95% CI 0.55–0.9), $p = 0.004$) and OS (HR = 0.74 (95% CI 0.56–0.97), $p = 0.027$). In the subgroup of *NPM1* wild type, only *IDH2* was associated with improved outcomes. In conclusion, our data suggest that *IDH1* and *IDH2* mutations are associated with improved outcomes in patients with AML undergoing allo-HCT in CR1.

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INTRODUCTION

The outcome of patients with acute myeloid leukemia (AML) has improved over the years, primarily due to a better understanding of the molecular and cytogenetic heterogeneity of AML and its prognostic implications [1–3]. More recently, three classification systems have updated the classification and risk stratification of AML based on recurrent genetic abnormalities [4–6]. However, several mutations have not yet been incorporated into the risk stratification, including isocitrate dehydrogenase 1 and 2 (*IDH1/2*) gene mutations, due to uncertainty regarding their prognostic implications.

IDH1/2 have been described in AML since 2008, when the first AML genome was sequenced [7]. They encode the isocitrate dehydrogenase enzymes. Mutations in these genes impair normal hematopoietic differentiation and promote leukemogenesis through competitive inhibition of αKG-dependent enzymatic

[1]Division of Hematology and Oncology and Blood and Marrow Transplantation and Cellular Therapy Program, University of Alabama at Birmingham, Birmingham, AL, USA. [2]Service d'Hematologie Clinique, Hopital Saint-Antoine, and INSERM UMRs 938, Paris, France. [3]Division of Hematology/Oncology, Columbia University Irving Medical Center/New York-Presbyterian Hospital, New York, NY, USA. [4]EBMT Paris Study Office, Saint Antoine Hospital, Paris, France. [5]Sorbonne University, Paris, France. [6]Institute of Hematology and Oncology, Hospital Clinic Barcelona, Barcelona, Spain. [7]University Hospital Eppendorf, Bone Marrow Transplantation Centre, Hamburg, Germany. [8]Erasmus MC Cancer Institute, University Medical Center Rotterdam, Department of Hematology, Rotterdam, The Netherlands. [9]Transplantation and Cellular Immunotherapy Program, Department of Hematology, Institut Paoli Calmettes, MSC Lab, Aix Marseille University, Marseille, France. [10]Hopital St. Louis, Dept.of Hematology-BMT, Paris, France. [11]Hôpital Henri Mondor, Service d'Hematologie, Creteil, France. [12]Hannover Medical School Department of Haematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover, Germany. [13]Oslo University Hospital, Hematology and Institute of Clinical Medicine University of Oslo, Oslo, Norway. [14]Dept. of Hematology, Leiden University Medical Center, Leiden, The Netherlands. [15]Gustave Roussy Cancer Campus BMT Service, Department of Hematology, Villejuif, France. [16]CHU Grenoble Alpes - Université Grenoble Alpes, Service d'Hématologie, Grenoble, France. [17]CHU de Lille, Univ Lille, INSERM U1286, Infinite, 59000 Lille, France. [18]Department of Medicine V, University Hospital Heidelberg, Heidelberg, Germany. [19]Universite Paris IV, Hopital la Pitié-Salpêtrière, Hématologie Clinique, Paris, France. [20]CHU Nantes Dept. D'Hematologie, Nantes, France. [21]Clinical Hematology Unit, Oncopôle, Toulouse, France. [22]Division of Hematology and Oncology, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon. [23]Tel Aviv University, BMT and Cord Blood Bank, Chaim Sheba Medical Center, Tel-Hashomer, Israel. [24]Hematology & Bone Marrow Transplant, IRCCS San Raffaele Scientific Institute, Milan, Italy. ✉email: rmohty@uabmc.edu

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activities [8, 9]. Approximately 20% of patients with AML carry *IDH1* or *IDH2* mutations [10]. They tend to present at an older age, have a higher blast percentage, carry a higher platelet count, and usually present with diploid or intermediate-risk cytogenetics [11]. Several studies evaluated the predictive and prognostic implications of *IDH1/2* mutations in AML [12, 13]. Despite being targetable mutations, the prognostic impact of *IDH1/2* mutations in AML remains controversial, which may explain their omission from AML risk stratification [14]. In a meta-analysis by Qingyu et al., including 12,747 patients with AML, overall survival (OS) and event-free survival (EFS) were worse in patients with *IDH1* mutation, whereas *IDH2* mutation was associated with favorable prognosis in terms of OS [15]. The uncertainty regarding the prognosis of patients with AML carrying *IDH1/2* mutations may be influenced by co-occurring mutations, notably *NPM1*, *DNMT3A*, and *FLT3* [16, 17]. For instance, *IDH*-mutated AML with *NPM1* co-mutation in the absence of *FLT3* mutation seems to carry a more favorable prognosis [18]. Studies assessing the outcomes of patients carrying these mutations in the allogeneic hematopoietic cell transplantation (allo-HCT) setting are limited to single center studies and/or include a small number of patients [19–21].

In this large retrospective registry-based analysis, we assessed the prognostic impact of *IDH1/2* mutations on patients with AML undergoing allo-HCT in first complete remission (CR1).

MATERIALS AND METHODS

Study design and eligibility criteria

This is a retrospective registry-based analysis of patients who underwent allo-HCT in CR1 between 2015 and 2022 and were reported to the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). The group comprises over 600 primarily European transplant centers, collecting data from consecutive HCTs in a centralized database. Independent systems are utilized for quality control purposes.

This retrospective study included 1515 consecutive patients from the EBMT registry who met the following inclusion criteria: a) adult (≥18 years) diagnosed with AML, b) recipient of allo-HCT between 2015 and 2022, c) allo-HCT at CR1, d) availability of reported information on *IDH1* or *IDH2* mutations. Cord blood transplants, ex-vivo graft manipulation, patients with favorable cytogenetics, and those with concomitant *IDH1* and *IDH2* mutations were excluded from the study due to limited numbers. Patients were divided into three groups based on *IDH1* and *IDH2* mutation status: no-IDH mutation, *IDH1* mutation, and *IDH2* mutation

Ethics approval and consent to participate

EBMT centers commit to obtaining informed consent according to the local regulations applicable at the time of transplantation to report pseudonymized data to the EBMT. The review committee of the ALWP of the EBMT registry approved this study. This retrospective analysis was conducted under the Declaration of Helsinki

Definitions

CR denotes complete hematologic remission. Leukemia-free survival (LFS) was defined as survival without evidence of relapse or progression. OS was defined as the time from intervention (allo-HCT) to death, regardless of the cause. Relapse was defined as leukemia recurrence at any site. Non-relapse mortality (NRM) was defined as death without any evidence of relapse or disease progression. Graft-versus-host disease (GVHD)-free, relapse-free survival (GRFS) was defined as time being alive with neither grade III-IV acute GVHD nor severe chronic GVHD nor disease relapse at any time point. Performance status was assessed using the Karnofsky performance status (KPS) score.

Statistical methods

The three groups were defined by the absence or presence of *IDH1* or *IDH2* mutations. Patient-, disease-, and transplant-related characteristics were compared between the three mutation status groups using the chi-square or Fisher's exact test for categorical variables and the Kruskal Wallis test for continuous variables. Probabilities of OS, LFS, and GRFS were calculated using the Kaplan-Meier method, and cumulative incidence (CI) curves were used for NRM, relapse, acute (a) and chronic (c) GVHD to accommodate for competing risks [22]. Death and relapse were considered competing events for GVHD. Univariate analyses were performed using the log-rank test for OS, LFS, GRFS, and Gray's test for CI estimates. A Cox proportional hazards model was used for multivariate regression. All variables differing significantly between the three groups and variables conceptually important, plus a center 'frailty' effect to take into account the heterogeneity across centers, were included in the Cox model [23, 24]. Results were expressed as the hazard ratio (HR) with a 95% confidence interval (95% CI). Tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed with SPSS 25.0 (SPSS Inc, Chicago, IL, USA) and R 4.2.3 (R Core Team, 2021, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients and disease characteristics

We identified 1515 consecutive adult patients with AML who had received allo-HCT in CR1. Patients were categorized into three groups according to *IDH1* and *IDH2* mutational status: 57.82% ($n = 876$) did not carry any of these mutations (no-IDH mutation), 15.91% ($n = 241$) had *IDH1* mutation (m*IDH1*), and 26.27% ($n = 398$) had *IDH2* mutation (m*IDH2*). The median age of all patients at the time of allo-HCT was 58.3 years (range, 18-77), with patients in the no-IDH group being of younger age ($p = 0.004$). Patients in the no-IDH group were more likely to be male compared to m*IDH1* and m*IDH2* groups (59.6% vs 55.8% vs 51.5%, $p = 0.025$), and carry poor risk cytogenetics (28.9% vs 19.1%, 18.1%, $p < 0.0001$), respectively. The no-IDH, m*IDH1*, and m*IDH2* groups were comparable with regard to donor source ($p = 0.83$), and intensity of the conditioning regimen (myeloablative conditioning [MAC], 44.1% vs 39.4% vs 42%, $p = 0.4$), respectively. Post-transplant cyclophosphamide (PTCy) was more likely to be used in the no-IDH compared to m*IDH1* and m*IDH2* groups (32.4% vs 27.9% vs 23.5%, $p = 0.005$), whereas in vivo T cell depletion was mainly used in the m*IDH2* groups (57.2% vs 61.3% vs 66.5%, $p = 0.007$), respectively. Minimal residual disease (MRD) data were available for 755 patients, 49.8% of which 334 (44.2%) were MRD-positive at time of allo-HCT. Patient, disease-, and transplant-related characteristics of both groups are summarized in Tables 1 and 2.

IDH1, *IDH2* and co-occurring mutations

IDH1 and *IDH2* mutations were more frequently encountered in middle-aged patients (40–59 years) (*no-IDH* 39.8%, m*IDH1* 48.5%, m*IDH2* 44.2%, $p < 0.0001$). Data were available for the co-occurring mutations: *FLT3-ITD*, *NPM1*, *ASXL1*, and *DNMT3A*. *NPM1* mutation was more frequent in the m*IDH1* group (no-IDH group, $n = 217$, 24.8%, m*IDH1*, $n = 103$, 42.7%, m*IDH2*, $n = 111$, 27.9%, $p < 0.0001$). Among patients with available data for *ASXL1* and *DNMT3A* mutations, *IDH1* and *IDH2* mutations were frequently associated with *ASXL1* (present in 20.3% in no-IDH group, 43.3% in m*IDH1 group and 36.9% in* m*IDH2 group* ; $p < 0.0001$) and *DNMT3A* mutations (35.4% in no-IDH, 86.5% in m*IDH1* and 75.6% in m*IDH2*; $p < 0.0001$) (Data not shown). However, no association were observed between *IDH1* and *IDH2*, and *FLT3-ITD* mutations (no-IDH group, 27.2% vs. m*IDH1*, 27.8% vs. m*IDH2*, 22.4%, $p = 0.15$) (Table 1).

Survival outcomes

The median duration of follow-up for the entire population was 23.5 (IQR, 21–26) months. The median duration of follow-up for the no-IDH, m*IDH1*, m*IDH2* groups was 24 (IQR, 22–26), 22 (IQR, 10–33), and 20 (IQR,13–27) months, respectively ($p = 0.11$) (Table 1). Overall, 364 (24%) patients died, 237 (27%) in the no-IDH, 44 (18%) in the m*IDH1*, and 83 (21%) in the m*IDH2* groups. The most common cause of death was disease relapse ($n = 158$, 46.7%), followed by infection ($n = 82$, 24.3%) and GVHD ($n = 51$, 15.1%) (results not shown).

Table 1. Patient and disease characteristics of all patients and according to mutation status group.

Patient characteristics	All patients	No IDH mutation	*IDH1* mutation	*IDH2* mutation	*p*-value
	N (%)	*N* (%)	*N* (%)	*N* (%)	
N	**1515**	**876**	**241**	**398**	
Follow-up, months [IQR]	23.5 [21–26]	24 [22–26]	22 [10–33]	20 [13–27]	0.11
Age at HSCT, Median [IQR]	58.3 [48.1–65.2]	57.2 [45.6–65.1]	58.6 [50–65.3]	59.2 [50.9–65.5]	**0.004**
18–39	217 (14.3%)	161 (18.4%)	18 (7.5%)	38 (9.5%)	**<0.0001**
40–59	642 (42.4%)	349 (39.8%)	117 (48.5%)	176 (44.2%)	
60+	656 (43.3%)	366 (41.8%)	106 (44%)	184 (46.2%)	
Patient Sex					
Male	861 (56.9%)	522 (59.6%)	134 (55.8%)	205 (51.5%)	**0.025**
Female	653 (43.1%)	354 (40.4%)	106 (44.2%)	193 (48.5%)	
FLT3-ITD					
No	1121 (74%)	638 (72.8%)	174 (72.2%)	309 (77.6%)	0.15
Yes	394 (26%)	238 (27.2%)	67 (27.8%)	89 (22.4%)	
NPM1					
No	1084 (71.6%)	659 (75.2%)	138 (57.3%)	287 (72.1%)	**<0.0001**
Yes	431 (28.4%)	217 (24.8%)	103 (42.7%)	111 (27.9%)	
Cytogenetics (per ELN2017)					
Intermediate	1144 (75.5%)	623 (71.1%)	195 (80.9%)	326 (81.9%)	**<0.0001**
Poor	371 (24.5%)	253 (28.9%)	46 (19.1%)	72 (18.1%)	
CMV patient					
Negative	592 (39.3%)	342 (39.3%)	94 (39.3%)	156 (39.3%)	1
Positive	914 (60.7%)	528 (60.7%)	145 (60.7%)	241 (60.7%)	
Missing	9	6	2	1	
Minimal residual disease					
No	421 (55.8%)	210 (54.3%)	78 (52%)	133 (61%)	0.16
Yes	334 (44.2%)	177 (45.7%)	72 (48%)	85 (39%)	
Missing	760	489	91	180	

IQR interquartile range, *IDH* isocitrate dehydrogenase, *HSCT* hematopoietic stem cell transplantation, *CMV* cytomegalovirus, *AML* acute myeloid leukemia, *ELN* European LeukemiaNet.
Bold values represent statistically significant findings.

Results of the multivariate analysis are shown in Table 3. The presence of *IDH2* mutation was associated with a lower risk of relapse (HR = 0.49 [95% CI 0.34–0.7], $p < 0.001$) (Fig. 1a), grade II-IV acute GVHD (HR = 0.73 [95% CI 0.56–0.96], $p = 0.025$) (Fig. 2a), which translated into a better LFS (HR = 0.7 [95% CI 0.55–0.9], $p = 0.004$) (Fig. 1c), GRFS (HR = 0.76 [95% CI 0.62–0.94], $p = 0.01$) (Fig. 2c), and OS (HR = 0.74 [95% CI 0.56–0.97], $p = 0.027$) (Fig. 1d) compared to the no-IDH group. The presence of *IDH2* mutation did not significantly impact NRM (HR = 1.05 (95% CI 0.74–1.48), $p = 0.8$) (Fig. 1b) or rate of chronic GVHD (HR = 0.87 [95% CI 0.68–1.11], $p = 0.26$) (Fig. 2b). *IDH1* mutation was associated with a lower rate of grade II-IV acute GVHD (HR = 0.66 [95% CI 0.47–0.91], $p = 0.011$) (Fig. 2a) and an improved OS (HR = 0.68 [95% CI 0.48–0.94], $p = 0.021$) compared to no-IDH (Fig. 1d). The presence of *IDH1* mutation did not significantly impact relapse (HR = 0.79 [95% CI 0.55–1.14], $p = 0.2$) (Fig. 1a), NRM (HR = 0.92 [95% CI 0.59–1.42], $p = 0.71$) (Fig. 1b), LFS (HR = 0.83 [95% CI 0.63–1.1]), $p = 0.19$) (Fig. 1c), GRFS (HR = 0.87 [95% CI 0.69–1.1], $p = 0.25$) (Fig. 2c), or chronic GVHD (HR = 0.87 [95% CI 0.65–1.17], $p = 0.36$) (Fig. 2c).

Variables associated with increased risk of relapse were adverse risk cytogenetics (HR = 1.88 [95% CI 1.43–2.48], $p < 0.0001$), presence of *FLT3-ITD* mutation (HR = 1.47 [95% CI 1.05–2.04], $p = 0.023$), and use of a matched sibling donor (MSD) (unrelated donor [UD] vs MSD, HR = 0.68 [95% CI 0.51–0.91], $p = 0.009$; haploidentical vs. MSD (HR = 0.61 [95% CI 0.4–0.93], $p = 0.021$). NRM was higher in patients with older age (HR per 10-year increment = 1.57 [95% CI 1.33–1.86], $p < 0.0001$), and improved in patients with a KPS ≥ 90% (HR = 0.62 [95% CI 0.45–0.84], $p = 0.002$). LFS was worse in patients with older age (HR = 1.11 [95% CI 1.02–1.21], $p = 0.013$), adverse risk cytogenetics (HR = 1.51 [95% CI 1.22–1.87], $p = 0.0002$), and presence of *FLT3-ITD* mutation (HR = 1.35 [95% CI 1.05-1.75], $p = 0.021$), and improved in patients with KPS ≥ 90% (HR = 0.76 [95% CI 0.62–0.94], $p = 0.011$). OS was worse in patients with older age (HR = 1.24 [95% CI 1.12–1.37], $p < 0.0001$), adverse risk cytogenetics (HR = 1.56 [95% CI 1.23–1.99], $p = 0.0003$) and presence of *FLT3-ITD* mutation (HR = 1.41 [95% CI 1.05–1.88], $p = 0.021$), and improved in patients with KPS ≥ 90% (HR = 0.76 [95% CI 0.62–0.94], $p = 0.011$).

Subgroup analyses: patients with NPM1-negative disease

In order to eliminate the positive effect of *NPM1* mutation, we conducted a similar analysis in the group of patients with *NPM1*-negative disease ($n = 1084$, 71.6%). In the multivariate analysis of the m*IDH1* group, there was a suggestion of improved OS (HR = 0.67 [95% CI 0.45–1.01], $p = 0.058$). Comparable to the entire cohort, presence of m*IDH1* did not impact relapse (HR = 0.84 [95% CI 0.55–1.29], $p = 0.43$), NRM (HR = 0.82 [95% CI 0.47–1.44], $p = 0.5$), LFS (HR = 0.84 [95% CI 0.59–1.17], $p = 0.3$), or GRFS (HR = 0.86 [95% CI 0.64–1.14], $p = 0.29$). Similarly, the presence of *IDH1* mutation decreased the risk of acute GVHD (HR = 0.65 [95% CI 0.43–0.99], $p = 0.044$). In the m*IDH2* group, comparable results were observed pertaining to lower risk of relapse (HR = 0.57 [95% CI 0.38–0.84], $p = 0.005$), improved LFS

Table 2. Transplant and donor characteristics for all patients and according to mutation status group.

Transplant characteristics	All patients	No IDH mutation	*IDH1* mutation	*IDH2* mutation	*p*-value
	N (%)	*N* (%)	*N* (%)	*N* (%)	
N	**1515**	**876**	**241**	**398**	
Year HSCT (range)	2020 (2015–2022)	2020 (2015–2022)	2020 (2015–2022)	2020 (2015–2022)	
HCT-CI score					
0	623 (45.2%)	356 (45.1%)	95 (43.4%)	172 (46.4%)	0.86
1-2	372 (27%)	207 (26.2%)	63 (28.8%)	102 (27.5%)	
>3	384 (27.8%)	226 (28.6%)	61 (27.9%)	97 (26.1%)	
Missing	136	87	22	27	
Female to male donor	250 (16.5%)	155 (17.7%)	37 (15.4%)	58 (14.6%)	0.34
CMV positive donor	741 (49.2%)	439 (50.4%)	125 (52.1%)	177 (44.9%)	0.12
Type of donor					
MSD	337 (22.2%)	196 (22.4%)	48 (19.9%)	93 (23.4%)	0.83
UD	924 (61%)	529 (60.4%)	152 (63.1%)	243 (61.1%)	
Haploidentical	254 (16.8%)	151 (17.2%)	41 (17%)	62 (15.6%)	
Stem cell source					
BM	85 (5.6%)	50 (5.7%)	15 (6.2%)	20 (5%)	0.8
PB	1430 (94.4%)	826 (94.3%)	226 (93.8%)	378 (95%)	
Conditioning intensity					
MAC	648 (42.8%)	386 (44.1%)	95 (39.4%)	167 (42%)	0.4
RIC	867 (57.2%)	490 (55.9%)	146 (60.6%)	231 (58%)	
GVHD prophylaxis					
Use of PTCY	441 (29.3%)	281 (32.4%)	67 (27.9%)	93 (23.5%)	**0.005**
In vivo T-cell depletion	910 (60.3%)	499 (57.2%)	147 (61.3%)	264 (66.5%)	**0.007**
CsA	258 (17.1%)	173 (19.8%)	28 (11.7%)	57 (14.4%)	
CsA + MTX	376 (24.9%)	191 (21.9%)	64 (26.7%)	121 (30.5%)	
MTX + Tacro	12 (0.8%)	4 (0.5%)	3 (1.2%)	5 (1.3%)	
CsA + MMF	604 (40%)	353 (40.5%)	104 (43.3%)	147 (37%)	
CsA + Tacro	3 (0.2%)	2 (0.2%)	0 (0%)	1 (0.3%)	
CsA + MTX + MMF	10 (0.7%)	3 (0.3%)	4 (1.7%)	3 (0.8%)	
Tacro + MMF	145 (9.6%)	82 (9.4%)	20 (8.3%)	43 (10.8%)	
MMF + Siro	22 (1.5%)	15 (1.7%)	4 (1.7%)	3 (0.8%)	
CsA + Tacro + MMF	6 (0.4%)	5 (0.6%)	0 (0%)	1 (0.3%)	
Tacro + Siro	9 (0.6%)	8 (0.9%)	1 (0.4%)	0 (0%)	
Other	64	36	12	16	
missing	6	4	1	1	

HSCT hematopoietic stem cell transplantation, *CR* complete remission, *HCT-CI* hematopoietic cell transplantation-specific comorbidity index, *CMV* cytomegalovirus, *BM* bone marrow, *PB* peripheral blood, *MSD* Matched sibling donor, *UD* unrelated donor, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *PTCY* post-transplant cyclophosphamide, *ATG* anti-thymocyte globulin, *GVHD* graft-versus-host disease, *CsA* cyclosporine, *MTX* methotrexate, *Tacro* tacrolimus, *MMF* mycophenolate mofetil, *Siro* sirolimus.
Bold values represent statistically significant findings.

(HR = 0.7 [95% CI 0.53–0.93], $p = 0.013$), OS (HR = 0.69 [95% CI 0.5–0.94], $p = 0.02$] and GRFS (HR = 0.78 [95% CI 0.61–0.99], $p = 0.04$). There was no impact on acute GVHD in the m*IDH2*, *NPM1*-negative subgroup (HR = 0.77 [95% CI 0.57–1.06], $p = 0.11$) (results not shown).

Engraftment and GVHD

The rate of engraftment was 98.7%, with only 19 (1.3%) patients experiencing graft failure in the entire group. Similar rates were observed in both the no-IDH ($n = 13$, 1.5%) and m*IDH2* ($n = 6$, 1.5%) groups ($p = 0.13$). No graft failure was observed in the m*IDH1 group*. (Results not shown).

At day 180, the CI of grade II-IV acute GVHD was significantly lower in m*IDH1* and m*IDH2* compared to no-IDH groups (21% vs. 20.8% vs. 28.8%, respectively, $p = 0.003$) (Fig. 2a). However, there was no significant difference in the CI of grade III-IV aGVHD at day 180 between the three groups (5.9% vs. 7.1% vs 8.9%, $p = 0.28$) (results not shown). No significant difference was noted in the 2-year CI of all grade chronic GVHD (38.1% vs. 37.7% vs. 40.1, $p = 0.52$) (Fig. 2b) and extensive chronic GVHD (19.9% vs. 19.4% vs. 18.4, $p = 0.95$) rates (results not shown) between the three groups, respectively.

DISCUSSION

This study represents one of the largest series evaluating the prognostic impact of *IDH1* and *IDH2* mutations on the outcomes of patients with AML undergoing allo-HCT. Our data suggest that the presence of *IDH1* or *IDH2* mutation are associated with improved outcomes in patients with AML undergoing allo-HCT in

Table 3. Multivariate analysis of AML outcomes after allo-HCT.

	RELAPSE		NRM		LFS		OS		GRFS		Acute GVHD II-IV		Acute GVHD III-IV		Chronic GVHD		Extensive chronic GVHD	
	HR (95% CI)	*p*-value	HR (95% CI)	*p* value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p* value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
No IDH mutation (ref)	**1**		**1**		**1**		**1**		**1**		**1**		**1**		**1**		**1**	
IDH1 mutation	0.79 (0.55–1.14)	**0.2**	0.92 (0.59–1.42)	**0.71**	0.83 (0.63–1.1)	**0.19**	0.68 (0.48–0.94)	**0.021**	0.87 (0.69–1.1)	**0.25**	0.66 (0.47–0.91)	**0.011**	0.65 (0.36–1.2)	**0.17**	0.87 (0.65–1.17)	**0.36**	1.04 (0.69–1.57)	**0.84**
IDH2 mutation	0.49 (0.34–0.7)	**<0.001**	1.05 (0.74–1.48)	**0.8**	0.7 (0.55–0.9)	**0.004**	0.74 (0.56–0.97)	**0.027**	0.76 (0.62–0.94)	**0.01**	0.73 (0.56–0.96)	**0.025**	0.81 (0.51–1.28)	**0.36**	0.87 (0.68–1.11)	**0.26**	1.02 (0.72–1.45)	**0.91**
Age (per 10 year)	0.95 (0.86–1.06)	0.36	1.57 (1.33–1.86)	**<0.0001**	1.11 (1.02–1.21)	**0.013**	1.24 (1.12–1.37)	**<0.0001**	1.08 (1–1.16)	**0.042**	1.06 (0.96–1.17)	0.24	1.04 (0.88–1.23)	0.64	0.98 (0.9–1.06)	0.61	1.04 (0.92–1.17)	0.57
Adverse cytogenetics	1.88 (1.43–2.48)	**<0.0001**	1.05 (0.73–1.52)	0.79	1.51 (1.22–1.87)	**0.0002**	1.56 (1.23–1.99)	**0.0003**	1.38 (1.14–1.66)	**0.0009**	1.17 (0.91–1.51)	0.21	1.2 (0.78–1.84)	0.4	1.07 (0.84–1.36)	0.57	1.34 (0.95–1.88)	0.094
FLT3-ITD	1.47 (1.05–2.04)	**0.023**	1.24 (0.83–1.86)	0.3	1.35 (1.05–1.75)	**0.021**	1.41 (1.05–1.88)	**0.021**	1.24 (0.99–1.54)	0.058	1.14 (0.86–1.5)	0.36	1.12 (0.67–1.86)	0.67	0.93 (0.71–1.22)	0.59	1.05 (0.71–1.54)	0.81
NPM1	0.72 (0.5–1.03)	0.069	0.9 (0.6–1.34)	0.6	0.78 (0.6–1.02)	0.073	0.8 (0.59–1.08)	0.15	0.79 (0.63–0.99)	0.04	1.03 (0.78–1.36)	0.81	0.65 (0.38–1.11)	0.12	0.98 (0.75–1.27)	0.87	1.01 (0.7–1.47)	0.94
MSD donor (ref)	1		1		1		1		1		1		1		1		1	
UD	0.68 (0.51–0.91)	**0.009**	1.21 (0.8–1.83)	0.37	0.85 (0.67–1.07)	0.18	1.01 (0.77–1.33)	0.92	0.83 (0.68–1.01)	0.069	1.39 (1.04–1.86)	**0.027**	1.08 (0.66–1.77)	0.76	0.84 (0.66–1.08)	0.17	0.68 (0.49–0.97)	**0.031**
Haploidentical	0.61 (0.4–0.93)	**0.021**	1.26 (0.74–2.14)	0.4	0.81 (0.59–1.12)	0.2	0.87 (0.6–1.26)	0.46	0.7 (0.53–0.92)	**0.011**	1.23 (0.85–1.79)	0.27	0.99 (0.53–1.88)	0.98	0.71 (0.5–0.99)	**0.046**	0.39 (0.23–0.64)	**0.0003**
Female to male	0.88 (0.63–1.24)	0.47	1.03 (0.7–1.54)	0.87	0.95 (0.73–1.22)	0.67	0.93 (0.7–1.25)	0.63	0.93 (0.74–1.16)	0.53	0.95 (0.71–1.28)	0.75	1.04 (0.63–1.72)	0.87	1.38 (1.07–1.78)	**0.013**	1.11 (0.76–1.63)	0.59
KPS ≥ 90	0.91 (0.69–1.21)	0.52	0.62 (0.45–0.84)	**0.002**	0.76 (0.62–0.94)	**0.011**	0.66 (0.53–0.83)	**0.0004**	0.75 (0.62–0.9)	**0.002**	0.88 (0.69–1.12)	0.3	0.72 (0.47–1.09)	0.12	1.07 (0.84–1.36)	0.6	0.79 (0.56–1.12)	0.18
In vivo TCD	0.92 (0.69–1.24)	0.58	1.07 (0.75–1.55)	0.7	0.97 (0.77–1.21)	0.77	0.78 (0.61–1)	0.054	0.68 (0.55–0.84)	**0.0004**	0.75 (0.56–1)	0.052	0.78 (0.49–1.26)	0.31	0.78 (0.6–1.02)	0.07	0.39 (0.26–0.58)	**<0.0001**
RIC vs MAC	1.12 (0.84–1.49)	0.44	1.18 (0.83–1.68)	0.36	1.17 (0.94–1.45)	0.17	1.17 (0.91–1.5)	0.21	1.1 (0.9–1.33)	0.36	1.14 (0.87–1.5)	0.33	0.82 (0.53–1.29)	0.4	1.12 (0.88–1.43)	0.36	1.15 (0.81–1.63)	0.43

ref referent group, *NRM* non-relapse mortality, *LFS* leukemia-free survival, *OS* overall survival, *GRFS* graft-versus-host disease-free, relapse-free survival, *GVHD* graft-versus-host disease, *HR* hazard ratio, *CI* confidence interval, *AML* acute myeloid leukemia, *CR* complete remission, *MSD* matched sibling donor, *UD* unrelated donor, *KPS* Karnofsky performance status, *TCD* T cell depletion, *RIC* reduced-intensity conditioning, *MAC* myeloablative conditioning.
Bold values represent statistically significant findings.

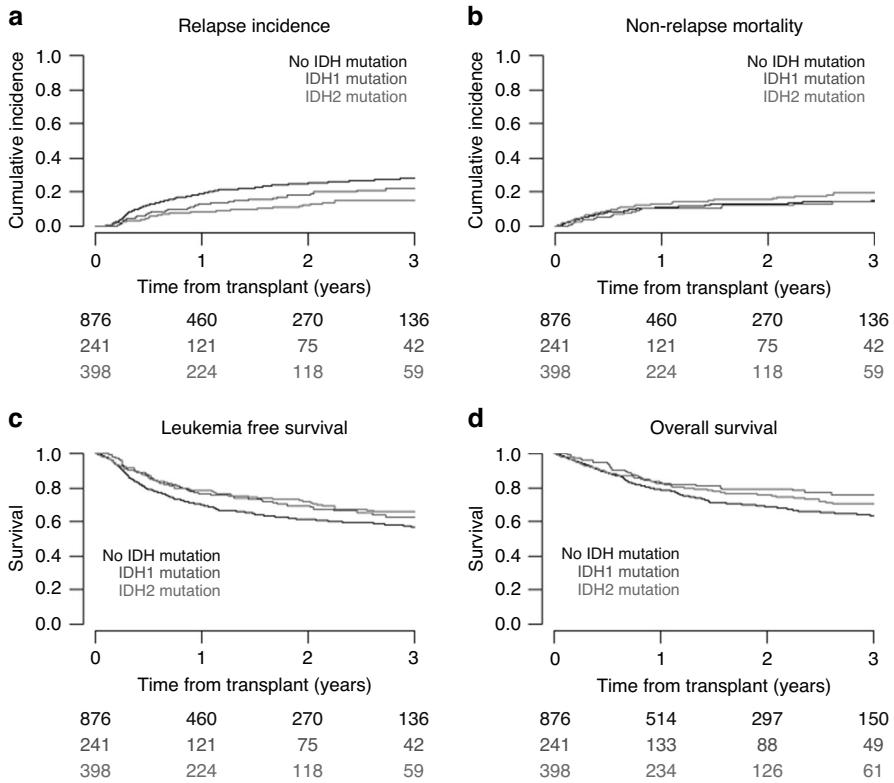

Fig. 1 Kaplan–Meier curves stratified by no *IDH* mutations, *IDH1* mutation, and *IDH2* mutation groups. a Relapse incidence, **b** non-relapse mortality, **c** leukemia-free survival, and **d** overall survival.

CR1. The impact of *IDH1* and *IDH2* mutations on outcomes of patients with AML has been inconsistent across studies. Meggendorfer et al. evaluated the outcomes of patients with *IDH1* or *IDH2* mutations compared to wild-type disease and found no difference in OS between presence or absence of *IDH* mutations ($p = 0.976$) [25]. A more detailed analysis of subgroup mutations found that *IDH2R172* mutation carries the best prognosis ($p = 0.040$). Similarly, Middeke et al. did not observe any difference in CR rate ($p = 0.17$), median relapse-free survival (RFS, $p = 0.52$) and OS ($p = 0.58$) between the *IDH* mutated and the wild-type groups. Yet, *IDH* mutational status was prognostic within the ELN2017 favorable risk group; the presence of *IDH1/2* mutations was associated with worse OS compared to no-IDH mutations ($p < 0.01$) [26].

Several studies have reported improved outcomes of patients with *IDH1/2* mutations in the setting of allo-HCT [20, 27]. Kunadt et al. evaluated the impact of *IDH1* and *IDH2* mutations on outcomes of patients with AML. When comparing allo-HCT vs. no allo-HCT in CR1, *IDH1R132C* and *IDH2R172* were associated with improved OS and RFS; *IDH2R132C* improved RFS. There was a trend towards improved OS with *IDH1R132H* and *IDH2R132H*. In the multivariate analysis, none of these mutations were associated with improved OS and RFS [20]. These results support the role of allo-HCT in CR1 in mitigating the unfavorable prognostic impact of specific *IDH* mutation subgroups. Chen et al. reported outcomes for 112 patients with *mIDH1/2* AML undergoing allo-HCT. They found an RFS of 58% in both *mIDH1* and *mIDH2* groups, with an OS of 74% for *mIDH1* and 68% for *mIDH2* groups [21]. Our cohort demonstrated a slightly higher LFS (69.6% and 71.8%) and OS (76% and 79.3%) in the *mIDH1* and *mIDH2* groups, respectively. In contrast to the study reported by Salhotra et al. [19], which found no survival difference between the presence or absence of *IDH* mutations in the transplant setting, we observed an improved OS in patients carrying *IDH1* or *IDH2* mutations.

In the ALPHA study, Duchman et al. reported that the presence of *IDH1* mutation was associated with a higher risk of relapse and reduced OS and *IDH2*R*172* mutation was associated with a higher risk of early death, whereas, the co-occurrence of *NPM1* mutation significantly improved OS [27]. In contrast, our results of positive prognostic impact of *IDH2* mutation remains consistent in the *NPM1* wild-type subgroup, unlike *IDH1* which showed only a favorable trend for improved outcomes in this subgroup. This observation suggests that *IDH2* mutation independently confers a better prognosis in patients undergoing allo-HCT compared to patients with wild-type disease. The improved prognostic impact of *IDH1* mutation may be potentially influenced by the presence of *NPM1* mutation.

Interestingly, in the multivariate analysis, the presence of *IDH1* mutation was associated with a significantly lower risk of acute GVHD. Similarly, the presence of *IDH2* mutation was associated with a significantly lower risk of acute GVHD, relapse, LFS, and OS. This unexpected benefit of *IDH1* and *IDH2* mutation in relation to the observed low incidence of acute GVHD in our study remains unexplained. There was no difference between the two groups with respect to baseline transplant characteristics that could impact GHVD occurrence, including donor type, stem cell source, and conditioning intensity. PTCy was more frequently used in the no-IDH group, and typically associated with lower incidence of GVHD. We speculate that this could possibly be due to the role of IDH as a key enzyme in the glycosylation and metabolic pathways on T cell function leading to the detected effect on GVHD [28]. Given the absence of any other explanation, further studies are warranted to investigate this finding.

Similar to previous reports, we observed a significant association between *IDH1/2* mutations and the co-occurrence of *NPM1*, *ASXL1*, and *DNMT3A* mutations, but not *FLT3-ITD*. In a study by Meggendorfer et al., the majority of patients with AML had co-occurring mutations ($n = 236$, 67%) [25]. The most frequent co-

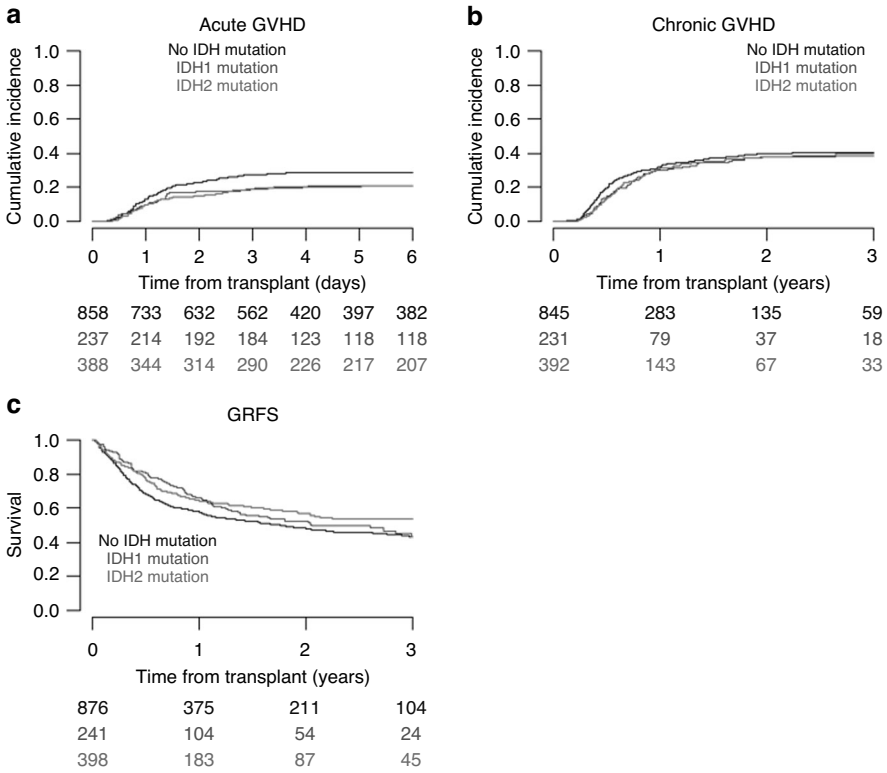

Fig. 2 Kaplan–Meier curves stratified by no *IDH* mutations, *IDH1* mutation, and *IDH2* mutation groups. a Cumulative incidence of acute GVHD, **b** cumulative incidence of chronic GVHD, and **c** GVHD-free relapse-free survival.

occurring mutation was *NPM1* (48%), followed by *DNMT3A* (42%), *SRSF2* (29%), *FLT3-ITD* (21%), and *ASXL1* (16%). Interestingly, in patients with *IDH1* and *IDH2* mutation, the presence of *NPM1* mutation significantly improved OS [25]. Additionally, in patients with *NPM1*-positive disease, the presence of *IDH2* mutation was associated with a decreased risk of relapse. Unlike prior studies, we observed a higher frequency of *IDH1 and IDH2* mutations in our cohort (42%) compared to previous reports (10–20%) [14, 29]. This discrepancy could be attributed to the selection bias of transplant-eligible patients rather than a population of newly diagnosed AML, thereby, excluding unfit patients for whom allo-HCT is not indicated. Additionally, it is important to highlight that the no-*IDH* mutation group was enriched with high-risk cytogenetics which could have influenced the results. A subgroup analysis was not possible due to the small number of patients in this subgroup.

In our study, we were able to evaluate the impact of MRD status on outcomes following allo-HCT. MRD positivity at the time of transplant was significantly associated with shorter LFS, highlighting the negative impact of MRD prior to allo-HCT on post-transplant outcomes. Conversely, Ravindra et al. did not show any prognostic impact of *IDH* MRD on leukemia relapse, RFS, and OS [30]. However, it is important to note that the latter study had a limited number of relapsed cases, and patients had received *IDH* inhibitors pre- and post-allo-HCT, which could have mitigated the impact of MRD on post-transplant outcomes. These findings emphasize the need to investigate the role of maintenance *IDH* inhibitors, especially in patients with MRD-positive disease. Preliminary results show safety and preliminary activity of maintenance enasidenib post allo-HCT [31]. Also, in the era of innovative artificial intelligence and machine learning, predictive models may hypothesize which patient would benefit most from this approach [32].

This study has certain inherent limitations due to its retrospective design. It is a registry study with lack of information on IDH inhibitor use pre- or post-allo-HCT, as first approval of IDH inhibitor was in 2017. MRD measurement technique was not reported and may have varied depending on center.

CONCLUSION

In conclusion, we found that *IDH1* and *IDH2*, in addition to being targetable mutations, carry prognostic implications, leading to improved outcomes of patients with AML undergoing allo-HCT. Our study showed a lower risk of relapse, and improved LFS and OS in patients with *IDH2* and improved OS in patients with *IDH1* mutated AML following allo-HCT, compared to patients without *IDH* mutations. Further studies investigating allo-HCT outcomes in *IDH1* and *IDH2* mutated patients with AML in the era of *IDH* inhibitors (both in the pre- and post-transplant setting) would help define the impact of these mutations in this setting and thus optimize an individualized treatment approach.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

RM wrote the manuscript, RM and MM designed the study, ML performed the statistical analysis, all authors reviewed its final version and were the principal investigators at the centers recruiting the highest number of patients into the study.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Razan Mohty.