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An adapted European LeukemiaNet genetic risk stratification for acute myeloid leukemia patients undergoing allogeneic hematopoietic cell transplant. A CIBMTR analysis

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Cytogenetic and molecular abnormalities are known to influence post-transplant outcomes in acute myeloid leukemia (AML) but data assessing the prognostic value of combined genetic models in the HCT setting are limited. We developed an adapted European LeukemiaNet (aELN) risk classification based on available genetic data reported to the Center for International Blood and Marrow Transplant Research, to predict post-transplant outcomes in 2289 adult AML patients transplanted in first remission, between 2013 and 2017. Patients were stratified according to aELN into three groups: favorable (Fav, $N = 181$), intermediate (IM, $N = 1185$), and adverse (Adv, $N = 923$). Univariate analysis demonstrated significant differences in 2-year overall survival (OS) (Fav: 67.7%, IM: 64.9% and Adv: 53.9%; $p < 0.001$); disease-free survival (DFS) (Fav: 57.8%, IM: 55.5% and Adv: 45.3; $p < 0.001$) and relapse (Fav: 28%, IM: 27.5% and Adv: 37.5%; $p < 0.001$). Multivariate analysis (MVA) revealed no differences in outcomes between the Fav and IM groups, thus they were combined. On MVA, patients in the Adv risk group had the highest risk of relapse (HR 1.47 $p \leq 0.001$) and inferior DFS (HR 1.35 $p < 0.001$) and OS (HR 1.39 $p < 0.001$), even using myeloablative conditioning or in those without the pre-HCT measurable-residual disease. Novel approaches to mitigate relapse in this high-risk group are urgently needed.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is an effective post-remission strategy for patients with acute myeloid leukemia (AML) in first complete remission (CR1). Due to considerable morbidity and mortality risk, careful consideration of patient [1] and disease-specific [2, 3] characteristics is required. Traditionally, biological stratification of AML risk has been based on cytogenetic findings at diagnosis [3, 4]. HCT in CR1 is considered for eligible patients with intermediate and high-risk cytogenetics whereas chemotherapy is recommended for those with favorable cytogenetics [2, 5, 6]. Approximately 45% of AML cases have a normal karyotype and cannot be subdivided based on cytogenetics; these patients have been assigned intermediate risk [4]. Subsequent identification of genomic mutations in AML, such as *FLT3*-ITD, *NPM1*, *CEBPA*, *MLL/KMT2A*, *IDH1-2*, *DNMT3A*, *TET2*, *TP53*, and *BCOR*

amongst others, has proven valuable for subdividing cytogenetically normal (CN) AML into subsets with different outcomes [7].

In 2010, the European LeukemiaNet (ELN2010) proposed a standardized prognostic system incorporating both cytogenetic and select molecular abnormalities (*CEBPA*, *NPM1*, and *FLT3*-ITD) to distinguish 4 distinct genetic risk groups [8]. Multiple studies confirmed the prognostic accuracy of ELN2010, applying it to patient cohorts receiving consolidation chemotherapy [9, 10] or HCT [11, 12]. In 2017, the ELN updated and simplified their classification (ELN2017) into 3-groups of favorable, intermediate, and adverse risk [13]. The new classification incorporated the addition of *RUNX1*, *ASXL1*, and *TP53* mutations to the adverse risk group, the inclusion of biallelic (but not monoallelic) *CEBPA* mutations to the favorable group, and stratification of *FLT3*-ITD on the basis of ITD-to-wild-type allelic ratio. Several groups have since

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applied ELN2017 to predict outcomes after chemotherapy [14–17] as well as compared the outcomes between ELN2010 and ELN2017 [14]. Single institution studies have also evaluated the utility of ELN2017 in predicting post-HCT outcomes [18, 19], but large, multicenter studies evaluating the impact of a combined genetic model exclusively in the transplant setting are lacking.

We analyzed data from the Center for International Blood and Marrow Transplant Research (CIBMTR) to evaluate the prognostic ability of an adapted ELN2017 model to predict allogeneic HCT outcomes.

MATERIALS AND METHODS
Data sources
Data were obtained from the CIBMTR which includes a voluntary network of over 500 transplantation centers worldwide that contribute detailed HCT data to a statistical center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program (NMDP®) Coordinating Center in Minneapolis. Participating centers are required to report all transplants consecutively; patients are followed longitudinally and compliance is monitored by on-site audits. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research subjects and approved by the National Marrow Donor Program® (NMDP)/Be The Match® Institutional Review Board. Protected Health Information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability Accountability Privacy Rule.

Patient selection
An initial cohort of 4777 adult patients (≥18 years) with a diagnosis of AML receiving their first allogeneic HCT between 2013 and 2017 and reported to the CIBMTR were included. Patients receiving a graft from a human leukocyte antigen (HLA)-matched sibling, fully matched unrelated donor, umbilical cord blood (UCB) graft, and haploidentical donors were eligible for the study. Patients with active disease (i.e., ≥5% bone marrow blasts prior to transplantation or those with evidence of extramedullary disease), remission status beyond CR1, a diagnosis of acute promyelocytic leukemia, and recipients of syngeneic or mismatched unrelated donor grafts were excluded.

Cytogenetic and molecular abnormalities present at the time of diagnosis or prior to initiation of the conditioning regimen were reported to the CIBMTR. When required, an additional review of reported genetic data was performed by three reviewers (AJ, DW, and KC) to adjudicate any uncertainties in classification. Cases with incomplete genetic data ($N =$ 152) were excluded. In addition, subjects with incomplete research consent forms and those from embargoed centers were also excluded. Ultimately, a cohort of 2289 transplant recipients from 163 centers was analyzed.

Cytogenetic and molecular classification
Patients were assessed for the presence of specific chromosomal and molecular abnormalities at diagnosis and prior to HCT. Cytogenetic data reported to the CIBMTR conformed to the International System of Cytogenetic Nomenclature [20]. The definition of complex karyotype (≥3 abnormalities) and monosomal karyotype were made according to previously published criteria. [21, 22].

Comprehensive molecular information (i.e., FLT3-ITD, NPM1, CEBPA, ASXL1, RUNX1, TP53, DNMT3A, BCR-ABL1, IDH1, and IDH2 mutational status obtained by next-generation sequencing [NGS] or PCR was reported to the CIBMTR beginning in 2013. Information regarding FLT3-ITD allelic ratio and CEBPA allelic status is not regularly reported to the CIBMTR and was therefore not included in our classification. On the basis of available registry molecular and conventional cytogenetic data, we defined an adapted ELN genetic risk stratification (aELN) (Table 1) whereby patients were stratified into three distinct groups: favorable (Fav, $N =$ 181), intermediate (IM, $N =$ 1185) and adverse (Adv, $N =$ 923).

The aELN classified patients with mutated NPM1 without FLT3-ITD and those with mutated CEBPA (without clarity of bi/mono allelic status) as favorable. Patients with mutated NPM1 with FLT3-ITD (irrespective of allelic ratio) and those with wild-type NPM1 without FLT3-ITD were classified as intermediate. Patients with FLT3-ITD (irrespective of allelic ratio) and wild-

Table 1. Adapted[a] ELN (aELN) risk stratification.

Favorable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
	Mutated NPM1 without FLT3-ITD
	Mutated CEBPA
Intermediate	Mutated NPM1 and FLT3-ITD
	Wild-type NPM1 without FLT3-ITD
	t(9;11)(p21.3;q23.3); MLLT3-KMT2A
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); DEK-NUP214
	t(v;11q23.3); KMT2A rearranged
	t(9;22)(q34.1;q11.2); BCR-ABL1
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
	−5 or del(5q); −7; −17/abn(17p); mutated TP53
	Complex karyotype (≥3 abnormalities)
	Monosomal karyotype
	Wild-type NPM1 and FLT3-ITD
	Mutated RUNX1 without good risk karyotype
	Mutated ASXL1 without good risk karyotype

[a]FLT3-ITD allelic ratio and CEBPA mono/bi-allelic status are not available.

type NPM1 were classified as adverse. Other chromosomal and molecular abnormalities were classified according to the 2017 ELN genetic risk criteria.

Study endpoints and variables
Disease-free survival (DFS, defined as time to relapse or death from any cause, with surviving patients in CR censored at last follow-up) was the study's primary endpoint. Secondary endpoints were: overall survival (OS, defined as time to death from any cause with surviving patients censored at last follow-up), non-relapse mortality (NRM, defined as death without preceding disease relapse/progression, relapse being a competing event), relapse (any reported events of leukemia relapse with NRM as competing event), acute and chronic graft vs. host disease (GVHD, with death as competing risk [23]). Patients were censored at subsequent HCT or last follow-up.

The study main effect was the influence of the aELN genetic risk group. Additional variables considered in the multivariate analysis (MVA) were: age at transplant, gender, race, Karnofsky performance score (KPS), HCT comorbidity index (HCT-CI), the clinical onset of AML (de novo vs. transformed vs. therapy-related), time to achieve first remission, measurable residual disease (MRD) status at transplantation, conditioning intensity, graft source, donor type and in vivo T-cell depletion (anti-thymocyte globulin [ATG] or alemtuzumab). Given intrinsic biologic and treatment-related differences between younger (i.e., <60 years) and older (i.e., ≥60 years) patients and previous reports demonstrating age-related differences in the distribution and impact of specific genetic abnormalities [9, 24], post-transplant outcomes were also analyzed separately between different age cohorts. We also identified the most commonly occurring abnormalities (i.e., reported in at least >100 patients) within the adverse aELN genetic group, and evaluated specific outcomes for these larger individual subsets.

Statistical analysis
Univariate analysis was performed using the Kaplan–Meier method and compared using the log-rank test for OS and DFS, while acute/chronic GVHD, NRM, and relapse used the cumulative incidence method considering competing risks, with comparisons performed using Gray's competing hazard method [25]. MVA was performed using the Cox proportional hazard model [26] for OS and DFS. The main effect of the aELN risk group was retained in all models. The assumption of proportional hazards for each factor in the Cox model was tested by adding time-

dependent covariates as necessary. When the test indicated differential effects over time (non-proportional hazards), models were constructed breaking the post-transplant time course into two periods, using the maximized partial likelihood method to find the most appropriate breakpoint. A backward stepwise model selection approach was used to identify significant risk factors. Factors that were significant at a 5% level were kept in the final model. Potential interaction between the main effect and significant co-variates was also tested for all endpoints. Adjusted probabilities of DFS and OS and adjusted cumulative incidence functions of NRM and relapse were calculated using the MVA models, stratified on the main effect, and weighted by the pooled sample proportion value for each prognostic factor. These adjusted probabilities estimate the likelihood of outcomes in populations with similar prognostic factors. All analyses were done using the statistical package SAS version 9.4 (Cary, NC).

RESULTS

Demographics
Baseline clinical features of all 2289 patients are presented in Table 2. The median age at HCT was 57.2 years (IQR 19.2–74.2 years). Importantly, 41% (936 patients) were ≥60 years, 76% (n = 1743) had de novo AML and 49% (1115) received a myeloablative conditioning (MAC) regimen. More patients in the Adv group (53% vs. 41.8% for Fav/IM patients, p < 0.001) had high HCT-CI. The frequency of secondary AML or therapy-related disease differed amongst groups (Fav 18.8%, IM 22.2%, and Adv 26.9%; p = 0.02). Pre-transplant measurable residual disease (MRD) was also significantly different between groups (Fav 21%, IM 11.5%, and Adv 22.9%; p < 0.001), however morphologic complete remission with incomplete blood count recovery (CRi) status was comparable for all cohorts (p = 0.29).

Of 923 patients with Adv risk, 380 (41.1%) had −5/del5q, or monosomy 7; 158 (17.1%) had wild-type NPM1 with mutated FLT3-ITD; 139 (15.06%) carried a t(v;11q23.3); KMT2A rearrangement and 137 patients (14.84%) had a complex karyotype (Table 3). Complex karyotype included all other Adv-risk patients (without del5/del7, wtNPM1 with FLT3-ITD or t(v;11q23.3) KMT2A rearrangement) having multiple (≥3) chromosomal abnormalities.

Transplant outcomes by aELN classification
Overall, 1237 of 2289 patients (54%) were alive at last follow-up with a median survival of 37 months (IQR, 24–51 months) and 1031 (83% of the survivors; 45% of the whole group) were alive and disease-free. The median follow-up for survivors was 35 months.

Disease relapse
Cumulative incidence of relapse at 2-years was 28% (95% confidence interval [CI], 21.5–35.1%), 27.5% (24.9–30.1%) and 37.5% (34.3–40.7%) for Fav, IM and Adv cohorts, respectively (p < 0.001) (Table 4 and Fig. 1C).

MVA confirmed that Adv risk patients had higher relapse rates (HR for Adv vs. Fav/IM: 1.47, 95% CI 1.28–1.70, p < 0.0001) with no differences observed between the Fav and IM groups; thus they were combined for subsequent analysis of other endpoints. Variables of interest considered in the MVA are listed in Supplemental Table S1.

Important variables independently associated with higher rates of relapse included: pre-transplant MRD (29.2% for MRD-negative [MRD^{neg}] vs. 42% for MRD-positive [MRD^{pos}]; HR: 1.47, 95% CI 1.23–1.76, p < 0.0001); AML onset (29.9% for de novo vs. 40.1% for secondary and therapy-related disease; HR: 1.43, 95% CI 1.19–1.72, p = 0.0001) and conditioning intensity (26.2% for MAC vs. 36.9% for non-myeloablative/reduced intensity regimens [NMA/RIC]; HR: 1.58, 95% CI 1.37–1.83, p < 0.0001, Supplemental Table S2).

While patients receiving RIC/NMA conditioning experienced higher rates of relapse, the impact of aELN Adv risk on relapse was observed for patients receiving either MAC or RIC/NMA (p < 0.001 for both).

Overall and DFS
There were significant differences in 2-year OS (Fav: 67.7% [95% CI, 60.5–74.6%], IM: 64.9% [62.1–67.6%] and Adv: 53.9% [50.6–57.2%]; p < 0.001) and DFS (Fav: 57.8% [95% CI, 50.3–65.2%], IM: 55.5% [52.6–58.4%] and Adv: 45.3% [42–48.6%]; p < 0.001) among aELN groups. (Table 4 and Fig. 1A, B). As above, Fav/IM were combined for further analysis.

The presence of pre-transplant MRD was associated with inferior 2-year OS (63.7% for MRD^{neg} vs. 46.6% for MRD^{pos}, p < 0.001) and DFS (54.4% for MRD^{neg} vs. 37.4% for MRD^{pos}, p < 0.001). MAC led to superior two-year DFS (57.2% vs. 46% for NMA/RIC regimens, p < 0.001) and OS (66% vs. 55.6% for MAC and NMA/RIC regimens, p < 0.001).

Adv aELN was shown on MVA to be a higher risk for both OS (HR for Adv vs. Fav/IM: 1.39, 95% CI 1.22–1.57, p < 0.001) and DFS (HR for Adv vs. Fav/IM: 1.35, 95% CI 1.20–1.51, p < 0.001, Table 5). Other variables independently associated with both OS and DFS included: age at HCT, pre-transplant MRD, donor type, the clinical onset of AML, and WBC at diagnosis (p ≤ 0.01 for all, Supplemental Table S2).

Non-relapse mortality and graft-versus-host disease
There were no significant differences in NRM among aELN groups (two-year NRM: Fav: 14.2% [95% CI, 9.3–19.8%], IM: 17.1 % [95% CI, 14.9–19.2%] and Adv: 17.3 % [95% CI, 14.9–19.8%]; p = 0.46). Similarly, aELN classification had no impact on the incidence of grade 2–4 acute GVHD (Fav: 30.9 % [95% CI, 24.4–37.9%], IM: 35.4 % [32.7–38.2%] and Adv: 35% [32–38.2%]; p = 0.42) or chronic GVHD (Fav: 40% [32.7–47.4%], IM: 43.6 % [40.7–46.6%] and Adv: 40.2% [37–43.5%]; p = 0.44).

Comparison of outcomes by aELN risk group and age
There were no significant differences in relapse rates among age groups (HR for Fav/IM ≥ 60 vs. <60: 1.19 [0.98–1.44] p = 0.08; HR for Adv ≥60 vs. <60: 1.17 [0.95–1.44] p = 0.15), but MVA confirmed higher NRM for older patients (≥60 y/o) in both Fav/IM (HR 1.40 [1.10–1.78] p = 0.007) and Adv risk cohorts (HR 1.59 [1.18–2.13] p = 0.002). Clinical outcomes were separately analyzed for two cohorts of younger patients (i.e., 18–39 vs. 40–59 years). MVA demonstrated inferior OS (HR 1.44 [1.18–1.75] p = 0.0003) and DFS (HR 1.23 [1.03–1.46] p = 0.02) for the 40–59 group. No significant differences in NRM or relapse were identified between these two younger cohorts. (Supplemental Table S2)

Outcomes by genetic subsets within the aELN Adv risk cohort
Genetic subset comparisons within the Adv-risk group showed that patients harboring monosomy 5, del[5q] or monosomy 7 (abnormal 5/7 subgroup) had inferior 2-year OS (42.6%, p < 0.001) and DFS (35.2%, p < 0.001), as well as higher rates of relapse (45%, p = 0.002) when compared to other patients within the Adv risk cohort (OS 60%, DFS 50.8%, relapse 33.5%).

Patients in the abnormal 5/7 subgroup were older (median age 59.8 [IQR 18.92–75.84] vs. 51.9 [IQR 18.9–73.7] for other Adv-risk patients, p < 0.001) and less often received MAC (45% vs. 56.4% MAC for other Adv-risk patients p < 0.001). Patients in the abnormal 5/7 subgroup also had a higher prevalence of pre-transplant MRD (28.4% vs. 19%, p = 0.003) when compared to other Adv risk patients (p < 0.001). MVA confirmed that abnormal 5/7 patients had higher relapse rates and inferior DFS and OS compared to other Adv risk patients (p < 0.0001 for all. Table 3B).

DISCUSSION
This large registry analysis of patients with AML undergoing allogeneic HCT demonstrates robust prognostic stratification by aELN in regard to relapse, DFS, and OS. Inferior survival in the Adv-risk cohort appears to be driven by higher relapse rates and ensuing inferior DFS. There were no significant interactions

Table 2. Patient, disease, and transplant characteristics.

Characteristic	Favorable	Intermediate	Adverse	P Value
No. of patients	181	1185	923	
No. of centers	66	144	125	
Patient-related				
Age at HCT—no. (%)				0.01[a]
Median (range) years	57.3 (18.4–73.5)	58.1 (19.6–74)	56.2 (19–74.4)	
18–29	12 (6.6)	97 (8.2)	104 (11.3)	
30–59	88 (48.6)	96 (48.9)	473 (51.3)	
60–69	63 (34.8)	417 (35.2)	287 (31.1)	
≥70	18 (9.9)	92 (7.8)	59 (6.4)	
Gender—no. (%)				0.16[a]
Male	95 (52.5)	615 (51.9)	517 (56)	
Female	86 (47.5)	570 (48.1)	406 (44)	
Race—no. (%)				<0.001[a]
Caucasian	138 (76.2)	942 (79.5)	718 (77.8)	
African-American	6 (3.3)	70 (5.9)	101 (10.9)	
Asian/Pacific Islander	27 (14.9)	110 (9.3)	70 (7.6)	
Other/missing	10 (5.6)	63 (5.3)	34 (3.7)	
Performance Score—no. (%)				0.09[a]
<90	64 (35.4)	434 (36.6)	386 (41.8)	
≥90	115 (63.5)	739 (62.4)	524 (56.8)	
Missing	2 (1.1)	12 (1)	13 (1.4)	
HCT-CI—no. (%)				<0.001[a]
0	39 (21.5)	245 (20.7)	171 (18.5)	
1–2	62 (34.3)	409 (34.5)	249 (27)	
3+	74 (40.9)	497 (41.9)	489 (53)	
Missing	6 (3.3)	34 (2.9)	14 (1.5)	
Disease-related				
White blood count at diagnosis, ×10^9/L				<0.001[a]
Median (range)	13.9 (0–270.5)	7.2 (0–329.7)	5 (0.4–290.9)	
≤10	73 (40.3)	597 (50.4)	528 (57.2)	
10–100	86 (47.5)	396 (33.4)	275 (29.8)	
>100	14 (7.7)	114 (9.6)	57 (6.2)	
Missing	8 (4.4)	78 (6.6)	63 (6.8)	
Clinical onset of AML—no. (%)				0.02[a]
De novo	147 (81.2)	922 (77.8)	674 (73)	
Transformed from MDS/MPN	23 (12.7)	188 (15.9)	161 (17.4)	
Therapy related	11 (6.1)	75 (6.3)	88 (9.5)	
CRi status pre-HCT—no. (%)				0.29[a]
Yes	49 (27.1)	328 (27.7)	269 (29.1)	
No	132 (72.9)	830 (70)	636 (68.9)	
Missing	0	27 (2.3)	18 (2)	
MRD pre-HCT[b]—no. (%)				<0.001[a]
No	128 (70.7)	917 (77.4)	666 (72.2)	
Yes	38 (21)	136 (11.5)	211 (22.9)	
Missing	15 (8.3)	132 (11.1)	46 (5)	

Table 2 continued

Transplant related				
Conditioning intensity—no. (%)				0.12[a]
MAC	91 (50.3)	547 (46.2)	477 (51.7)	
RIC/NMA	90 (49.7)	637 (53.8)	446 (48.3)	
Missing	0	1 (0.1)	0	
Graft type—no. (%)				0.62[a]
Bone marrow	34 (18.8)	173 (14.6)	135 (14.6)	
Peripheral blood	119 (65.7)	827 (69.8)	635 (68.8)	
Cord blood	28 (15.5)	185 (15.6)	153 (16.6)	
Donor type—no. (%)				0.68[a]
HLA-identical sibling	49 (27.1)	325 (27.4)	223 (24.2)	
Other related	14 (7.7)	99 (8.4)	69 (7.5)	
Haploidentical	23 (12.7)	124 (10.5)	117 (12.7)	
HLA-Matched unrelated (8/8)	67 (37)	452 (38.1)	361 (39.1)	
Cord blood	28 (15.5)	185 (15.6)	153 (16.6)	
GVHD prophylaxis—no. (%)				0.24[a]
Ex vivo T-cell depletion/CD34 selection	10 (5.5)	49 (4.1)	55 (6)	
PTCy	24 (13.3)	179 (15.1)	158 (17.1)	
TAC based	111 (61.3)	713 (60.2)	554 (60)	
CSA based	33 (18.2)	230 (19.4)	149 (16.1)	
Other	3 (1.7)	14 (1.2)	7 (0.8)	
In vivo T-cell depletion—no. (%)				0.46[a]
No	137 (75.7)	944 (79.7)	733 (79.4)	
ATG/Alemtuzumab	44 (24.3)	241 (20.3)	190 (20.6)	
Year of HCT—no. (%)				0.15[a]
2013	34 (18.8)	220 (18.6)	139 (15.1)	
2014	36 (19.9)	275 (23.2)	237 (25.7)	
2015	36 (19.9)	278 (23.5)	208 (22.5)	
2016	47 (26)	248 (20.9)	188 (20.4)	
2017	28 (15.5)	164 (13.8)	151 (16.4)	
Follow-up of survivors—median (range) months	24.6 (0.4–62.8)	35.3 (0.2–69.4)	35.1 (0.4–63.3)	

AML acute myeloid leukemia, *ATG* anti-thymocyte globulin, *CMV* cytomegalovirus, *CRi* complete remission with incomplete blood count recovery, *CSA* cyclosporine, *HCT* hematopoietic cell transplant, *HiDAC* high-dose cytarabine, *HMA* hypomethylating agent, *IDAC* intermediate-dose cytarabine, *MAC* myeloablative conditioning, *MDS* myelodysplastic syndrome, *aELN* adapted European LeukemiaNet, *MMF* mycophenolate mofetil, *MPN* myeloproliferative neoplasm, *MRD* measurable residual disease, *NMA* non-myeloablative, *PTCy* post-transplant cyclophosphamide, *RIC* reduced-intensity conditioning, *TAC* tacrolimus.
Hypothesis testing:
[a]Pearson chi-square test.
[b]MRD was assessed by different methods including, but not limited to: next-generation sequencing (NGS), polymerase chain reaction (PCR) testing, chromosomal/genomic microarray analysis, fluorescence in situ hybridization (FISH), karyotyping, flow cytometry.

between the main effect of aELN risk group and any significant risk factors. This confirms that the aELN classification is applicable to all patients receiving HCT in CR1, both younger (<60 years) and older (≥60 years) and for patients with de novo and transformed/secondary AML. In addition, the impact of adverse genetics is not overcome by greater conditioning intensity.

Previous reports examining the prognostic ability of ELN2017 as compared to ELN2010 support the new combined genetic prognostic model for treatment of newly diagnosed AML patients [14–17] and a recent single-institution analysis also evaluated the prognostic impact of ELN2017 following HCT [18]. Some of these studies are limited by patient heterogeneity, small sample sizes, or different consolidation strategies. We assessed the impact of a combined genetic model exclusively in the transplant setting and restricted our analysis to patients receiving allogeneic HCT in CR1. While the effect of genetic abnormalities continues to be important

beyond CR1, prior relapse, particularly early relapse, carries a heavier prognostic weight than most genetic abnormalities [27].

Fav and IM risk groups were combined in our study after pairwise multivariate analysis demonstrated no significant differences in any outcomes. This could, in part, be explained by a smaller number of Fav-risk AML patients proceeding to HCT in CR1, but perhaps most importantly by the presence of non-genetic, adverse clinical features in the Fav risk cohort (i.e., elevated WBC at diagnosis, failed induction, pre-transplant MRD, etc.) which could have resulted in early transplantation referral. Thus, due to inherent clinical differences between Fav patients referred to HCT and those with the newly diagnosed disease, aELN distinguished only two (and not three) distinct prognostic groups in the HCT setting.

Despite inferior outcomes compared to the Fav/IM group, the overall survival for Adv patients was still 52% at 2 years, a modest

Table 3. A. Adverse-risk patient characteristics by genetic subgroups. B. Multivariate analysis of outcomes. Comparison of abnormal 5/7 subgroup vs. other adverse aELN risk groups[a].

A. Adverse-risk patient characteristics by genetic subgroups

Characteristic	Abnormal 5/7	[a]Others	P Value
No. of patients	380	543	
Age at HCT—no. (%)			<0.001[b]
Median (range)	59.81 (18.98–75.84)	51.92 (18.96–73.76)	
18–59	195 (51.3)	382 (70.3)	
≥60	185 (48.7)	161 (29.7)	
Conditioning intensity—no. (%)			<0.001[b]
MAC	171 (45)	306 (56.4)	
RIC/NMA	209 (55)	237 (43.6)	
MRD at time of HCT—no. (%)			0.003[b]
No	255 (67.1)	411 (75.7)	
Yes	108 (28.4)	103 (19)	
Missing	17 (4.5)	29 (5.3)	
CRi status prior to conditioning—no. (%)			0.06[b]
Yes	127 (33.4)	142 (26.2)	
No	246 (64.7)	390 (71.8)	
Missing	7 (1.8)	11 (2)	

B. Multivariate Analysis of Outcomes. Comparison of abnormal 5/7 subgroup vs. Other adverse aELN risk groups

	HR (95% CI)	*p*-Value
Overall survival	1.58 (1.32–1.90)	<0.0001
Disease-free survival	1.54 (1.30–1.83)	<0.0001
Relapse	1.59 (1.28–1.97)	<0.0001

CRi complete remission with incomplete blood count recovery, *GVHD* graft-vs.-host disease, *HCT* hematopoietic cell transplant, *MAC* myeloablative conditioning, *aELN* adapted European LeukemiaNet, *MRD* measurable residual disease, *NMA* non-myeloablative, *RIC* reduced-intensity conditioning.
[a]Reference group. Includes wt*NPM1* with *FLT3*-ITD, t(v;11q23.3), *DEK-NUP214*, complex karyotype, *BCR-ABL1*, GATA2, *MECOM*, mutated *TP53*, non-del5/del7 monosomy, mutated *RUNX1/ASXL1* without good-risk karyotype
[b]Pearson chi-square test

Table 4. Univariate outcomes by aELN risk group.

	Favorable (N = 181)		Intermediate (N = 1185)		Adverse (N = 923)		
Outcomes	N	Prob (95% CI)	N	Prob (95% CI)	N	Prob (95% CI)	P Value
Overall survival[a]	181		1185		923		<0.001
		67.7 (60.5–74.6)%		64.9 (62.1–67.6)%		53.9 (50.6–57.2)%	
Disease-free survival[a]	178		1170		910		<0.001
		57.8 (50.3–65.2)%		55.5 (52.6–58.4)%		45.3 (42–48.6)%	
Relapse[a]	178		1170		910		<0.001
		28 (21.5–35.1)%		27.5 (24.9–30.1)%		37.5 (34.3–40.7)%	
Non-relapse mortality[a]	178		1170		910		0.467
		14.2 (9.3–19.8)%		17.1 (14.9–19.3)%		17.3 (14.9–19.8)%	
Grade II–IV acute GVHD[b]	181		1171		913		0.423
		30.9 (24.4–37.9)%		35.4 (32.7–38.2)%		35 (32–38.2)%	
Chronic GVHD[a]	181		1177		918		0.442
		40 (32.7–47.4)%		43.6 (40.7–46.6)%		40.2 (37–43.5)%	

GVHD graft-vs.-host disease, *aELN* adapted European LeukemiaNet.
Outcomes at:
[a]2 years.
[b]100 days.
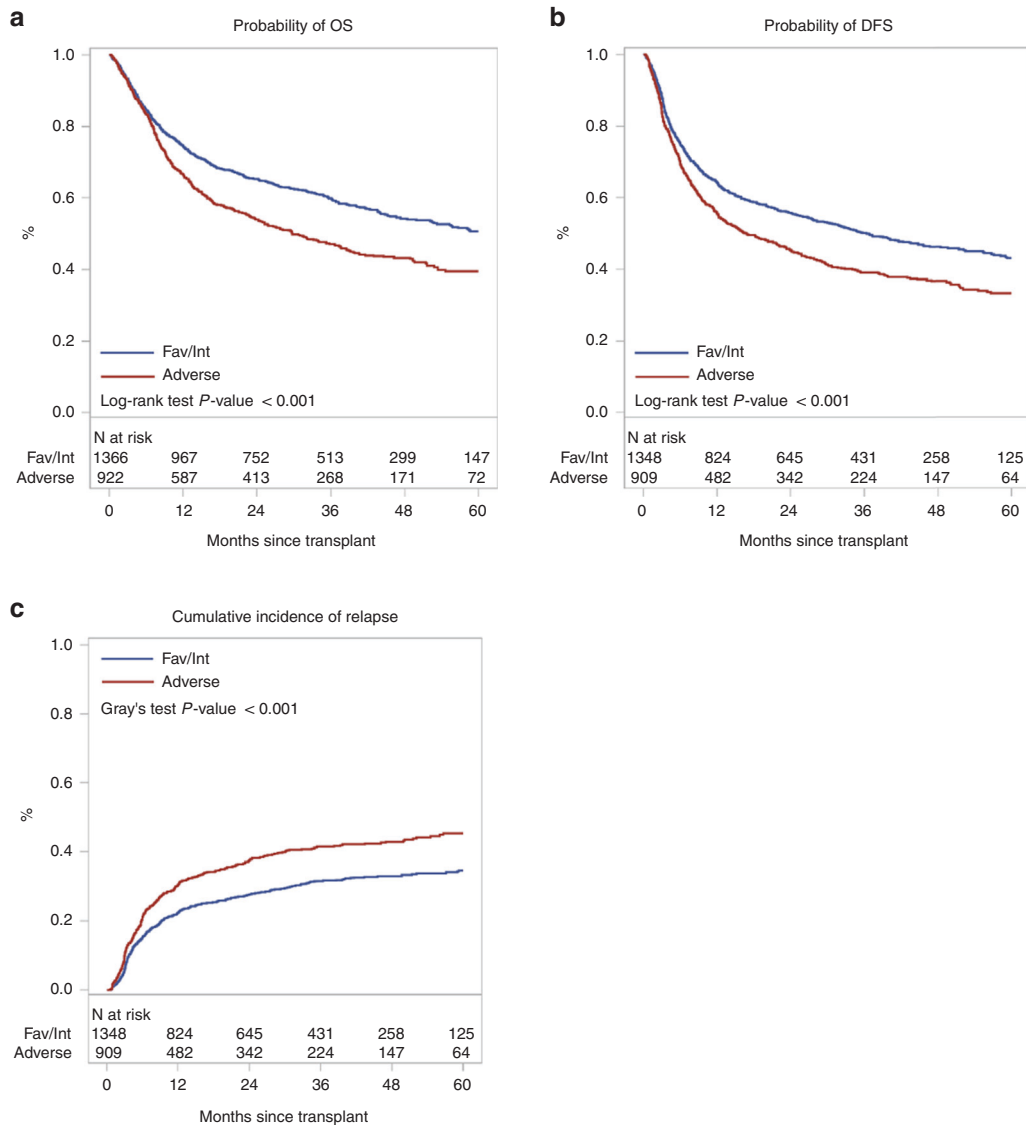
Fig. 1 Transplant outcomes by aELN classification. OS (**A**), DFS (**B**), and cumulative incidence of disease relapse (**C**) for AML transplant recipients within favorable/intermediate vs. adverse aELN cohorts.

Table 5. Multivariate analysis of outcomes. Comparison of adverse vs. favorable/intermediate[a] aELN risk groups.

	HR (95% CI)	*p*-Value
Overall survival	1.39 (1.22–1.57)	<0.001
Disease-free survival	1.35 (1.20–1.51)	<0.001
Relapse	1.47 (1.28–1.70)	<0.001
Non-relapse mortality	1.01 (0.81–1.19)	0.89
Grade II–IV acute GVHD	1.04 (0.91–1.19)	0.53
Chronic GVHD	0.95 (0.83–1.08)	0.42

GVHD graft-vs.-host disease, *aELN* adapted European LeukemiaNet.
[a]Reference group.

difference from the Fav/IM group; but most importantly, significantly better than reported without allogeneic HCT. Herold and colleagues recently validated the ELN2017 risk stratification among 1116 adult AML patients enrolled on two multicenter phase III trials of the German AML Cooperative Group [16]. Two-year survival for Adv patients was 22.1% (20.6% following chemotherapy or autoHCT consolidation for patients in CR1). Several cooperative and single-institution studies have also reported very poor outcomes for Adv risk patients receiving post-remission therapies other than allogeneic HCT [14, 15]. While clear differences in outcomes were noted between Adv and Fav/IM groups, prognostic separation was clear when either was compared to patients receiving non-transplant consolidation. It is not unreasonable to suggest that allogeneic transplantation could have a partial "equalizing" effect amongst different genetic subsets.

We identified the most commonly occurring genetic abnormalities (i.e., >100 cases) within the Adv aELN group. As reported, [18, 28] we confirmed that patients carrying monosomy 5, del[5q] or monosomy 7 (abnormal 5/7) had significantly higher rates of post-transplant relapse and inferior survival, even when transplanted in CR1. Monosomy 7 was the most common individual abnormality reported, with worse outcomes noted in the context of monosomal karyotype. Patients in the abnormal 5/7 subgroup were older and received less aggressive conditioning; however, the adverse impact of 5/7 was seen across all age groups and also in patients receiving MAC.

Unfortunately, we could not assess in our analysis the clinical impact of post-transplant maintenance and preemptive strategies in our cohort or elucidate the indications for HCT in Fav/IM risk

patients. Additional study limitations were intrinsic to a retrospective cohort analysis, including incomplete genetic data for some patients and a lack of uniformity for MRD assessment methods among multiple institutions.

The impact of pre-HCT MRD has been previously reported by several groups [29–32]. The presence of MRD correlates with increased post-transplant relapse, particularly in patients receiving RIC/NMA regimens. While we observed a higher proportion of pre-HCT MRD in the Adv aELN group, the presence of MRDpos was independently associated with higher post-HCT relapse across the aELN subsets. The patients in this study were transplanted prior to the publication of the ELN consensus guidelines for AML MRD assessment however, even without interlaboratory or detection technology standardization, residual disease pre-HCT was consistently associated with more relapse.

In conclusion, this adapted ELN classification had prognostic value for survival and relapse after allogeneic HCT. Novel peri-transplant pre-emptive and therapeutic strategies to reduce relapse remain necessary for all groups, but particularly those within the Adv cohort, those at highest risk.

DATA AVAILABILITY
CIBMTR supports the accessibility of research in accord with the National Institutes of Health (NIH) Data Sharing Policy and the National Cancer Institute (NCI) Cancer Moonshot Public Access and Data Sharing Policy. The CIBMTR only releases de-identified datasets that comply with all relevant global regulations regarding privacy and confidentiality.

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COMPETING INTERESTS

ADDITIONAL INFORMATION

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