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RESEARCH ARTICLE

Challenging the Adverse Label: Diverse Outcomes of ELN 2022 Adverse Cytogenetic Subgroups in Acute Myeloid Leukemia Patients Allografted in First Remission: From EBMT ALWP

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ABSTRACT

According to the European LeukemiaNet (ELN) 2022 classification, acute myeloid leukemia (AML) patients with intermediate or adverse risk are offered allogeneic hematopoietic stem cell transplantation (allo-HSCT) in first remission. In this EBMT study, we included 1735 adult AML patients with ELN-2022 adverse-risk cytogenetics allografted between 2010 and 2022 in first remission (67% de novo AML, median age 56 years). Eleven non-overlapping adverse-risk cytogenetics groups were defined. The five most frequent were: Group 1 [$n = 394$; monosomy 17 or abn(17p); 2-year leukemia-free survival (LFS) 22%, and overall survival (OS) 25%]; Group 2 [$n = 313$; complex karyotype (CK) involving monosomy 5, monosomy 7, or del(5q) without monosomy 17 or abn(17p); LFS 27%, OS 37%]; Group 3 [$n = 201$; monosomy 5, monosomy 7, or del(5q) without CK and without monosomy 17 or abn(17p); LFS: 55%, OS: 63%]; Group 4 [$n = 256$; CK without monosomal karyotype (MK) or adverse additional cytogenetic abnormalities (ACA); LFS 50%, OS 61%]; Group 5 [$n = 213$; t(v, 11q23) without adverse ACA; LFS 50%, OS 59%]. In multivariable analysis, compared to CK without adverse ACA, LFS was negatively affected by monosomy 17 or 17p abnormalities, monosomy 5, 7, or del(5q) in the presence of CK, and t(8;16). In conclusion, this study revealed a very poor outcome of allografted AML patients with monosomy 17 or 17p abnormalities or CK involving monosomy 5, monosomy 7, and del5q. Outcomes were relatively favorable for most other ELN 2022 adverse categories, including CK with or without MK other than 5, 7, and 17, indicating that allo-HSCT can overcome their poor outcome.

1 | Introduction

The presence of cytogenetic abnormalities continues to serve as an important factor in determining clinical outcomes for patients newly diagnosed with acute myeloid leukemia (AML). Recognizing and comprehensively assessing cytogenetic abnormalities not only serves as diagnostic markers but also guides therapeutic decisions. Risk groups in AML are classified into three categories according to the 2022 European LeukemiaNet (ELN) risk stratification based on genetics [1]. Currently, according to the ELN 2022 classification, patients falling into the intermediate- or adverse-risk categories are typically offered allogeneic hematopoietic stem cell transplantation (allo-HSCT) in the first complete remission (CR1) [2].

The updated classification includes some changes in the cytogenetic criteria associated with adverse-risk, notably the addition of those involving specific genetic alterations such as t(3q26.2;v) affecting the *MECOM* gene and t(8;16)(p11;p13) linked with *KAT6A::CREBBP* [3–5]. In addition, hyperdiploid karyotypes, distinguished by the presence of multiple trisomies (or polysomies), are presently omitted from the complex karyotype (CK) classification [6]. Integrating cytogenetic alterations with other prognostic factors is also essential when dealing with patients categorized as adverse-risk [7].

While the ELN 2022 adverse-risk karyotypes have been previously analyzed in the general AML population [8–11], their frequency and prognostic relevance in the specific context of allo-HSCT in CR1 have not been comprehensively evaluated. Using a large dataset from the European Society for Blood and Marrow Transplantation (EBMT) registry, we aimed to evaluate the real-world implications of the AML ELN 2022 adverse cytogenetic risk classification on the prediction of relapse and survival in patients receiving allo-HSCT in CR1, regardless of somatic mutation status.

2 | Patients and Methods

2.1 | Study Design and Inclusion Criteria

This is a retrospective, registry-based, multicenter analysis of patients' data provided and approved by the Acute Leukemia Working Party (ALWP) of the EBMT. The EBMT is a voluntary working group of more than 600 transplant centers that are required to report all consecutive HSCTs and follow-ups once a year. Audits are routinely performed to determine the accuracy of the data. Since January 2003, all transplant centers have been required to obtain written informed consent prior to data registration with the EBMT, following the guidelines of the Declaration of Helsinki, 1975.

We included in this analysis, adult patients (≥ 18 years) with AML and with availability of full karyotype at diagnosis, classified as ELN 2022 adverse cytogenetic risk, who received their first allo-HSCT in CR1, between 2010 and 2022, from either a matched sibling donor (MSD), matched or mismatched unrelated donor (UD), haploidentical donor, or cord blood. The stem cell source was either granulocyte colony-stimulating factor mobilized peripheral blood (PB), bone marrow, or cord blood.

Variables collected included recipient age at transplant, recipient and donor gender, karyotype at diagnosis, *NPM1, FLT3*-ITD, *CEBPA*, and *TP53* mutation status at diagnosis, time from diagnosis to transplant, year of transplant, measurable residual disease (MRD) status at transplant, Karnofsky performance status score at transplant, hematopoietic cell transplant-specific comorbidity index, in addition to transplant-related factors including conditioning regimen, graft-versus-host disease (GVHD) prophylaxis, the use of post-transplant cyclophosphamide (PTCy), in vivo T-cell depletion, donor type, recipient and donor cytomegalovirus status, and stem cell source (PB or bone marrow).

2.2 | Definitions

Cytogenetics was reported by full karyotype, using the International System for Human Cytogenomic Nomenclature (ISCN) guidelines. Adverse-risk cytogenetic subgroups were classified according to the ELN 2022 but considered only cytogenetic features. As defined in the ELN2022: CK consisted of three or more abnormalities; however, hyperdiploid karyotypes, distinguished by the presence of multiple trisomies (or polysomies), are presently omitted from the CK classification. Monosomal karyotype (MK) was defined as the presence of two or more distinct monosomies (excluding loss of X or Y) or one single autosomal monosomy in combination with at least one structural chromosome abnormality.

Conditioning intensity was measured using the transplant conditioning regimen intensity myeloablative conditioning/reduced intensity conditioning (RIC) classification [12] and transplant conditioning intensity score [13]. Myeloablative conditioning was defined as a regimen containing either total body irradiation with a dose greater than 6 Gy, a total dose of oral busulfan greater than 8 mg/kg, or a total dose of intravenous busulfan greater than 6.4 mg/kg or treosulfan greater than 36 g/m^2. All other regimens were defined as RIC. The diagnosis and grading of acute and chronic GVHD were performed by transplant centers using standard criteria [14].

2.3 | Statistical Analysis

Quantitative variables are described as median, quartiles 1 and 3, minimum, and maximum. Qualitative variables are described as numbers and percentages.

To evaluate the associations between 10 individual cytogenetic abnormalities (including adverse 3q26), secondary AML, and the monosomal and complex nature of karyotypes, we performed a multiple correspondence analysis (MCA).

MCA is a statistical technique that allows simultaneous assessment of relationships between multiple qualitative variables. It transforms the matrix of patients and categorical variables into a numerical format, capturing the greatest variability in the data within the first few dimensions. Each patient is assigned a set of values, with the first two dimensions accounting for the most significant variability.

Using these two dimensions, we created a two-dimensional graphical representation of the patients. Each variable modality (e.g., presence or absence of a specific cytogenetic abnormality) is represented by its centroid (barycenter), providing a visual summary of their relationships. The final output is a graphical representation of the different modalities across the first two dimensions of the 13 analyzed variables.

This multidimensional approach provides a comprehensive overview of how variables are linked. Interpretation is based on spatial proximity: when two modalities appear close to each other, it indicates they are frequently observed together in the same patients.

Endpoints included leukemia-free survival (LFS), overall survival (OS), non-relapse mortality (NRM), relapse incidence (RI), acute and chronic GVHD, and GVHD-free and relapse-free survival (GRFS). All outcomes were measured from the time of allo-HSCT. LFS was defined as survival without leukemia relapse or progression; patients alive without leukemia relapse or progression were censored at the time of last contact. OS was defined as death from any cause. NRM was defined as death without previous leukemia relapse. GRFS was defined as survival without grade III–IV acute GVHD, extensive chronic GVHD, relapse, or death. The probabilities of OS, LFS, and GRFS were calculated using the Kaplan–Meier method. Cumulative incidence functions were used to estimate RI, NRM, and GVHD outcomes in a competing risk setting. Death and relapse were considered as competing events for acute and chronic GVHD. Univariate comparisons were performed using the log-rank test for LFS, OS, and GRFS, and Gray's test for cumulative incidences. Cox proportional-hazards models were built to evaluate the impact of cytogenetics groups adjusted on age at HSCT, donor type, year of HSCT, Karnofsky score, intensity of the conditioning regimen (myeloablative/RIC), and nature of the AML (de novo/secondary). Potential center effects have been taken into account as frailty. The Type-1 error rate was fixed at 0.05. All analyses were performed using R 4.1.1 (R Development Core Team, Vienna, Austria, URL:https://www.R-project.org/). The MCA has been performed using the R package FactoMineR.

3 | Results

3.1 | Patient and Transplant Characteristics

We identified 1735 adult AML patients with ELN 2022 adverse-risk cytogenetics allografted in CR1 between 2010 and 2022. Patients and transplant characteristics are summarized in Table 1. Most of these patients had de novo AML (67%), with a median age of 56 years (range: 18–78), and 52% were male. At diagnosis, *NPM1* and *FLT3*-ITD were mutated in 6% and 12% of patients with available data, respectively. In patients with available MRD data, 234 patients (39%) were MRD positive and 373 (61%) were MRD negative at transplant. Karnofsky performance status was less than 90 in 499 patients (30%). Patients received primarily RIC (54%) and PB stem cells (88%) from an MSD (24%), UD (57%), or haploidentical donor (17%). Approximately 60% of patients received in vivo T-cell depletion, while PTCy was given to 20% of patients. Almost two-thirds of the patients (62%) and nearly half of the donors (48%) were cytomegalovirus positive.

3.2 | Frequency of Adverse Cytogenetic Abnormalities

Eleven distinct nonoverlapping adverse-risk cytogenetic groups were defined and ranked by decreasing frequency (Table 1).

Group 1 ($n = 394$) comprised cases with monosomy 17 or abn(17p), irrespective of adverse additional cytogenetic abnormalities (ACA). In more detail (Figure 1A, Table S1), monosomy 17 was present in 67% of the patients and abn(17p) in 38%. Only 17 patients had simultaneously a monosomy 17 and an abn(17p). Regarding the other adverse features, karyotypes were almost always CK (96%), predominantly associated with MK (90%), monosomy 7 (35%), del(5q) (36%), and monosomy 5 (30%). The other adverse abnormalities were present in less than 1% of cases.

Group 2 ($n = 313$) included cases with CK involving monosomy 5 (20%), monosomy 7 (46%), or del(5q) (54%) but without monosomy 17 or abn(17p), regardless of adverse ACA. Regarding the other adverse features, MK was present in 81%, adv(3q26) in 12%, t(9;22) in 2%, and the other adverse abnormalities in less than 1% of cases.

Group 3 ($n = 201$) included monosomy 5, monosomy 7, or del(5q) without CK and without monosomy 17 or abn(17p). In 48% of cases, the abnormality was isolated; 36% had MK, and 16% had only one other abnormality. The second adverse abnormality was t(9;22) for two patients.

Group 4 ($n = 256$) included CK without MK or other known adverse ACA, while Group 5 ($n = 213$) featured t(v;11q23) translocations without adverse ACA other than CK or MK. In that group, for 52% of the patients, the abnormality was isolated, 21% had one other nonadverse abnormality, 25% had CK, less than 1% MK without CK, and 1% CK and MK. Group 6 ($n = 178$) included CK with MK (excluding abnormalities involving chromosomes 5, 7, or 17) and no other adverse ACA. Group 7 ($n = 58$) included abn(3q26) without adverse ACA other than t(9;22) which was present in 10% of cases. Group 8 ($n = 50$) was defined by t(6;9) without other adverse ACA, and this abnormality was isolated for 90% of cases. Group 9 ($n = 43$) included cases with t(9;22) without other adverse ACA. The abnormality was isolated for 44% of cases. Group 10 ($n = 15$) included MK (excluding abnormalities of chromosomes 5, 7 and 17) without other adverse ACA. Finally, Group 11 ($n = 14$) included t(8;16) without adverse ACA. The abnormality was isolated in 43% of cases.

Patients and transplant characteristics for each of these 11 cytogenetic groups are presented in Table 1. Clinically defined secondary AML was more frequent in the monosomy 5/7/del(5q) not CK group (47%) and the t(8;16) group (57%), and was as follows in other groups: CK involving monosomy 5/7/del(5q) (41%), the monosomy 17/abn(17p) group (41%), CK without MK group (27%), CK with MK group (30%), and the abn(3q26) group (35%). In contrast, it was infrequent in the t(v;11q23) group (13%), the t(6;9) group (12%), the t(9;22) group (19%), and the MK group (7%). Older age (median above 55 years) was more commonly observed in the monosomy 5/7/del(5q), monosomy 17/abn(17p), CK with and without MK, and abn(3q26) groups. *FLT3*-ITDs were more frequent in the t(6;9) group (65%), and to a lesser extent in the CK without

TABLE 1 | Baseline patient and transplant characteristics according to adverse-risk cytogenetics group.

Variables	Modalities	All patients	Mono17,abn17p	Complex Mono7,5,del5q (not mono17 or abn17p)	Mono7,5,del5q (not complex–mono17 or abn17p)	Complex	t(v,11q23)	Complex monosomal	abn3q26+/−t(9;22)	t(6;9)	t(9;22)	Monosomal (not 5,7,17)	t(8;16)
	No. patients	1735	394	313	201	256	213	178	58	50	43	15	14
Patient sex	Female	829 (48)	174 (44)	150 (48)	110 (55)	119 (46)	111 (52)	85 (48)	27 (47)	25 (50)	12 (28)	8 (53)	8 (57)
Age at HSCT	Median (rg)	56 (18–78)	59 (19–74)	60 (19–76)	58 (18–77)	51 (18–78)	43 (18–74)	55 (18–74)	56 (26–72)	45 (21–71)	46 (19–69)	48 (18–68)	45 (18–67)
Type of AML	de novo	1156 (67)	232 (59)	184 (59)	107 (53)	186 (73)	185 (87)	125 (70)	38 (66)	44 (88)	35 (81)	14 (93)	6 (43)
	Sec AML	579 (33)	162 (41)	129 (41)	94 (47)	70 (27)	28 (13)	53 (30)	20 (34)	6 (12)	8 (19)	1 (7)	8 (57)
MRD	Negative	373 (61)	82 (64)	53 (54)	37 (51)	52 (62)	72 (81)	30 (60)	12 (67)	18 (64)	9 (29)	6 (40)	2 (67)
	Positive	234 (39)	46 (36)	45 (46)	35 (49)	32 (38)	17 (19)	20 (40)	6 (33)	10 (36)	22 (71)	0 (0)	1 (33)
	Missing	1128	266	215	129	172	124	128	40	22	12	9	11
Donor sex	Female	606 (35)	141 (36)	150 (48)	110 (55)	88 (34)	63 (30)	71 (40)	17 (29)	16 (32)	14 (33)	6 (40)	6 (43)
F-M	Yes	278 (16)	75 (19)	45 (14)	25 (13)	39 (15)	27 (13)	36 (20)	8 (14)	9 (18)	8 (19)	3 (20)	3 (21)
KPS	≥90	1158 (70)	266 (70)	206 (68)	135 (71)	181 (74)	143 (72)	106 (64)	37 (68)	34 (68)	29 (71)	8 (57)	13 (93)
Source of cells	PB	1515 (88)	354 (90)	279 (89)	177 (88)	221 (87)	179 (84)	152 (85)	50 (88)	45 (90)	35 (81)	10 (67)	13 (93)
	BM	128 (7)	24 (6)	19 (6)	15 (8)	15 (6)	23 (11)	13 (7)	6 (10)	3 (6)	6 (14)	3 (20)	1 (7)
	CB	43 (2)	11 (3)	8 (3)	6 (3)	8 (3)	2 (1)	3 (2)	1 (2)	2 (4)	2 (5)	0 (0)	0 (0)
	Others	49 (2)	5 (1)	6 (2)	3 (1)	12 (4)	9 (3)	10 (5)	1 (2)	0 (0)	0 (0)	2 (13)	0 (0)
Donor type	MSD	417 (24)	105 (27)	71 (23)	37 (18)	61 (24)	55 (26)	43 (24)	12 (21)	13 (26)	12 (28)	3 (20)	5 (36)
	Haplo	295 (17)	58 (15)	48 (15)	31 (15)	46 (18)	39 (18)	34 (19)	11 (19)	11 (22)	9 (21)	7 (47)	1 (7)
	M. Relative	19 (1)	2 (1)	2 (1)	2 (1)	6 (2)	2 (1)	0 (0)	1 (2)	1 (2)	1 (2)	0 (0)	0 (0)
	UD	988 (57)	226 (57)	187 (60)	128 (64)	141 (55)	116 (54)	99 (55)	34 (59)	24 (48)	20 (47)	5 (34)	8 (57)
	UCB	16 (1)	3 (1)	3 (1)	3 (2)	2 (1)	1 (0)	2 (2)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)
MAC	Yes	795 (46)	156 (40)	107 (34)	88 (44)	136 (53)	116 (56)	93 (52)	25 (44)	32 (65)	27 (63)	7 (47)	8 (57)
TBI	Yes	332 (19)	65 (16)	66 (21)	41 (20)	40 (16)	47 (22)	35 (20)	12 (21)	10 (20)	9 (21)	4 (27)	3 (21)
In vivo TCD	No	682 (40)	155 (39)	125 (40)	76 (38)	107 (42)	79 (37)	68 (38)	22 (39)	20 (41)	17 (40)	9 (60)	4 (29)
	ATG	927 (54)	215 (55)	167 (54)	104 (52)	134 (53)	115 (54)	95 (54)	31 (54)	26 (53)	25 (58)	6 (40)	9 (64)
	Campath	113 (7)	24 (6)	18 (6)	19 (10)	12 (5)	17 (8)	14 (8)	4 (7)	3 (6)	1 (2)	0 (0)	1 (7)

(Continues)

TABLE 1 | (Continued)

Variables	Modalities	All patients	Mono17,abn17p	Complex Mono7,5,del5q (not mono17 or abn17p)	Mono7,5,del5q (not complex–mono17 or abn17p)	Complex	t(v,11q23)	Complex monosomal	abn3q26+/−t(9;22)	t(6;9)	t(9;22)	Monosomal (not 5,7,17)	t(8;16)
Ex vivo TCD	Yes	49 (3)	5 (1)	5 (2)	6 (3)	11 (4)	7 (4)	8 (5)	2 (4)	2 (4)	1 (2)	1 (8)	1 (7)
PTCY	Yes	335 (20)	75 (19)	66 (21)	39 (20)	61 (24)	35 (17)	21 (12)	10 (18)	13 (26)	9 (21)	5 (33)	1 (7)
Patient CMV	Positive	1073 (62)	236 (60)	205 (66)	115 (56)	160 (62)	124 (60)	121 (68)	36 (63)	30 (60)	26 (62)	10 (71)	10 (71)
Donor CMV	Positive	817 (48)	175 (45)	154 (50)	85 (43)	124 (49)	103 (51)	90 (51)	28 (49)	27 (54)	18 (42)	6 (40)	7 (50)
NPM1	Absent	761 (94)	168 (97)	131 (96)	98 (94)	112 (89)	96 (96)	86 (92)	20 (100)	24 (92)	13 (76)	7 (88)	6 (100)
	Present	50 (6)	5 (3)	6 (4)	6 (6)	14 (11)	4 (4)	8 (8)	0 (0)	2 (8)	4 (24)	1 (12)	0 (0)
	Missing	924	221	176	97	130	113	84	38	24	26	7	8
FLT3ITD	Absent	759 (88)	170 (93)	131 (93)	102 (91)	117 (88)	94 (89)	89 (88)	19 (95)	12 (35)	12 (80)	8 (80)	5 (100)
	Present	101 (12)	13 (7)	10 (7)	10 (9)	16 (12)	12 (11)	12 (12)	1 (5)	22 (65)	3 (20)	2 (20)	0 (0)
	Missing	875	211	172	89	123	107	77	38	16	28	5	9
CEBPA	Absent	406 (94)	94 (96)	72 (99)	52 (88)	54 (93)	55 (95)	38 (86)	11 (100)	15 (100)	8 (100)	4 (80)	3 (100)
	Present	26 (6)	4 (4)	1 (1)	7 (12)	4 (7)	3 (5)	6 (14)	0 (0)	0 (0)	0 (0)	1 (20)	0 (0)
	Missing	1303	296	240	142	198	155	134	47	35	35	10	11
TP53	Absent	137 (41)	15 (12)	16 (24)	24 (89)	25 (71)	26 (100)	16 (47)	5 (100)	8 (89)	1 (100)	0 (0)	1 (100)
	Present	194 (59)	110 (88)	51 (76)	3 (11)	10 (29)	0 (0)	18 (53)	0 (0)	1 (11)	0 (0)	1 (100)	0 (0)
	Missing	1404	269	246	174	221	187	144	53	41	42	14	13

Abbreviations: abn: abnormality; AML: acute myeloid leukemia; ATG: anti-thymocyte globulin; BM: bone marrow; CB: cord blood; CMV: cytomegalovirus; F-M: female to male; haplo: haplo-identical donor; HSCT: hematopoietic stem cell transplantation; KPS: Karnofsky performance status; M: matched; MAC: myeloablative conditioning; Mono: monosomy; MRD: measurable residual disease; MSD: matched sibling donor; PB: peripheral blood; PTCy: post-transplant cyclophosphamide; rg: range; Sec: secondary; TBI: total body irradiation; TCD: T-cell depletion; UCB: unrelated cord blood; UD: unrelated donor.

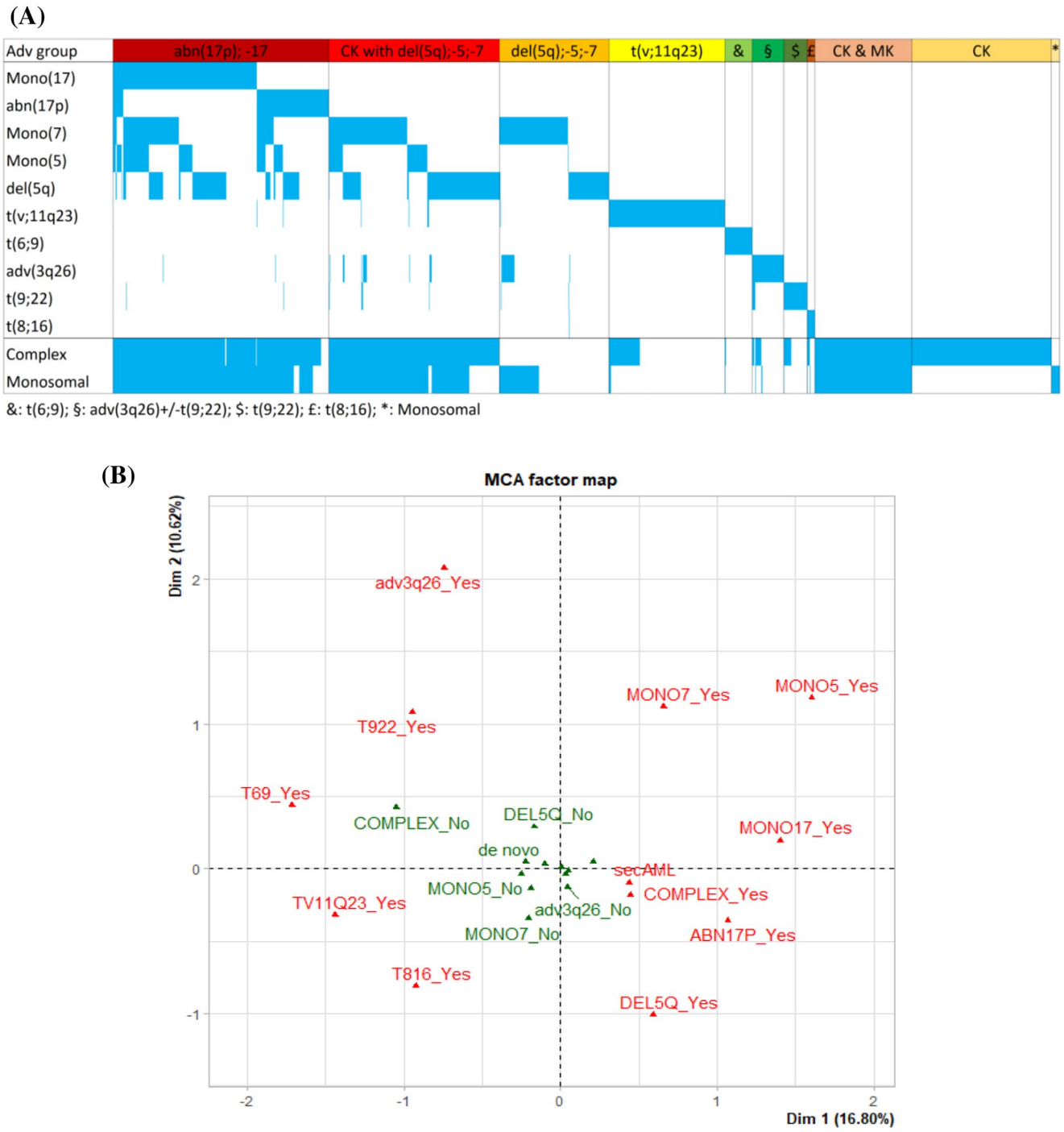

FIGURE 1 | (A) Frequency of the various individual adverse cytogenetic abnormalities in the whole cohort and according to cytogenetic subcategory. (B) Multiple correspondence analysis. This plot graphically depicts the associations between 13 different variables, including cytogenetic subgroup and AML type. The most significant correlated cytogenetic subgroups are highlighted in red. Monosomy 5, 7, and 17 are very close. Also, complex karyotype, 17p abnormality, and del5q are close to each other and are associated with secondary AML; the third group, which includes adv(3q26), t(6;9) and t(9;22), is also close to each other; the fourth group includes t(v,11q23) and t(8;16).

MK (12%), the CK with MK group (12%), t(9;22) group (20%), and the MK group (20%). *TP53* mutations were more frequent (88%) in monosomy 17/abn(17p) patients, and in monosomy 5/7/del(5q) with CK (76%).

The frequency of the various adverse cytogenetic abnormalities in the whole cohort as well as in each of the 11 groups is presented in Figure 1A and Table S1.

3.3 | Multiple Correspondence Analysis

We then performed a MCA in order to have the global overview of the associations between the 10 groups of ACA, including also the CK and secondary AML indicators. We can observe on the MCA four categories of co-occurring cytogenetic abnormalities: the first category includes monosomy 5, 7, and 17; the second includes CK, 17p abnormality, and del5q; the third includes

TABLE 2 | Overall survival, leukemia-free survival, relapse incidence, non-relapse mortality, incidence of GVHD, and GRFS according to cytogenetic subcategory.

Variable	Modalities	2 years OS % [95% CI]	2 years LFS % [95% CI]	2 years RI % [95% CI]	2 years NRM % [95% CI]	100 days AGVH II–IV % [95% CI]	100 days AGVH III–IV % [95% CI]	2 years GRFS % [95% CI]
Cytogenetic subcategory	Complex	60.8 [53.7–67.2]	49.9 [42.8–56.5]	34.9 [28.4–41.4]	15.2 [10.7–20.4]	23.8 [18.6–29.3]	9.4 [6.2–13.5]	39.8 [33–46.5]
	Complex_monosomal	54.9 [46.6–62.4]	47.5 [39.4–55.1]	34.8 [27.4–42.4]	17.7 [12.2–24]	26.3 [20–33.1]	10.5 [6.5–15.6]	35.8 [28.2–43.5]
	Mono17,abn17p	25.2 [20.5–30.2]	21.7 [17.3–26.5]	62.2 [56.6–67.2]	16.1 [12.4–20.2]	25.4 [21.2–29.9]	11 [8.1–14.4]	14.9 [11.1–19.3]
	Not complex Mono7,5,del5q (wo mono17 or abn17p)	62.9 [54.7–70]	54.9 [46.9–62.1]	29.5 [22.7–36.7]	15.6 [10.7–21.3]	27.3 [21.1–33.7]	7.4 [4.2–11.6]	41.8 [34.1–49.2]
	Complex Mono7,5,del5q (wo mono17 or abn17p)	36.7 [30.8–42.6]	27.2 [21.8–32.8]	51 [44.7–56.9]	21.9 [17.2–26.9]	24.9 [20.2–29.8]	9 [6.2–12.5]	20 [15.2–25.3]
	t(8;16)	39.3 [14.5–63.6]	39.3 [14.5–63.6]	45.7 [17.4–70.4]	15 [2–39.9]	7.1 [0.4–28.5]	7.1 [0.4–28.5]	34.2 [10.7–59.8]
	abn3q26+/−t(9;22)	51.1 [36.1–64.2]	40.6 [27.2–53.5]	40.8 [27.3–53.8]	18.6 [9.5–30.2]	22.6 [12.4–34.7]	5.7 [1.5–14.2]	30.5 [18.8–43.1]
	t(9;22)	77.7 [58.2–88.9]	66.1 [47.4–79.4]	25.9 [12.4–41.7]	8 [1.9–19.9]	31 [17.7–45.2]	11.9 [4.3–23.7]	61.1 [42.6–75.3]
	Monosomal not 5,7,17	73.3 [43.6–89.1]	73.3 [43.6–89.1]	6.7 [0.4–27.1]	20 [4.5–43.3]	33.3 [9.4–60]	16.7 [2.3–42.5]	34.3 [11.6–58.7]
	t(6;9)	69.6 [52.1–81.8]	66.4 [49.2–78.9]	14.1 [5.5–26.6]	19.6 [8.8–33.4]	40.4 [26.3–54.1]	14.9 [6.5–26.6]	53 [36.3–67.2]
	t(v,11q23)	58.8 [51.1–65.7]	49.5 [42–56.6]	35.3 [28.4–42.3]	15.1 [10.4–20.7]	21.7 [16.3–27.6]	9.4 [5.9–13.9]	38 [30.9–45.2]
	p	< 0.001	< 0.001	< 0.001	0.36	0.42	0.93	< 0.001

Abbreviations: abn: abnormal; AGVH: acute graft versus host disease; CI: confidence interval; GRFS: graft-versus-host and relapse-free survival; LFS: leukemia-free survival; mono: monosomy; NRM: non-relapse mortality; OS: overall survival; RI: relapse incidence.

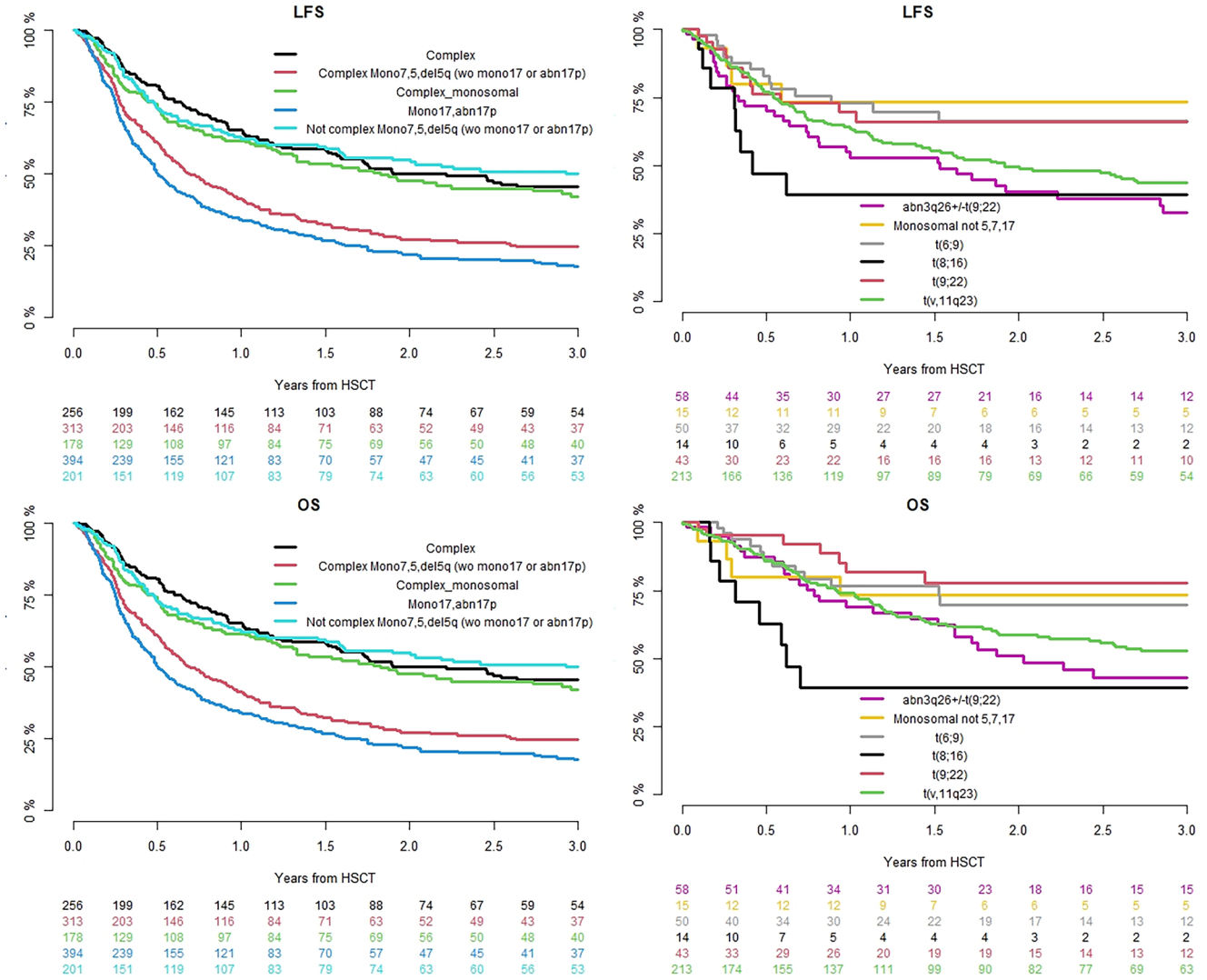

FIGURE 2 | Leukemia-free survival and overall survival curves according to cytogenetic subcategories. HSCT: hematopoietic stem cell transplant; LFS: leukemia-free survival; OS: overall survival.

abv(3q26), t(6;9) and t(9;22); the fourth includes t(v,11q23) and t(8;16). The MCA is shown in Figure 1B.

3.4 | Outcome Analysis According to Adverse Cytogenetic Abnormalities

Median follow-up was 3 years. Overall, the 2-year RI, LFS, and OS were 43%, 40%, and 48%, respectively. Post-transplant outcomes according to the 11 groups of adverse cytogenetic abnormalities are summarized in Table 2 and Figures 2 and 3. Outcomes were relatively poor for patients in Group 1 with monosomy 17/abn(17p) with 2-year RI, LFS, and OS of 62%, 22%, and 25%, respectively, and Group 2 with monosomy 5/7/del(5q) and CK: 51%, 27%, and 37%, respectively. Conversely, outcomes of patients with CK without adverse ACA were relatively favorable with 2-year LFS and OS of 50% and 61% in the absence of MK and 48% and 55% in the presence of MK other than chromosomes 5, 7, and 17.

3.5 | Multivariable Analysis

In the multivariable analysis (Table 3), compared to the group of CK without adverse ACA, RI, LFS, OS, and GRFS were negatively affected by monosomy 17/abn(17p) (hazard ratio [HR] 2.65, 2.21, 2.41, and 2.05, respectively, all $p < 0.001$) and Group 2 with CK involving monosomy 5/7/del(5q) (HR 1.81, 1.77, 1.86, and 1.66, respectively, all $p < 0.001$). LFS and OS were negatively affected by the presence of t(8;16) (HR 2.02; $p = 0.04$ and 2.81; $p = 0.003$, respectively) while OS was better in the t(9;22) group (HR 0.43; $p = 0.03$). Finally, compared to MSD grafts, RI was significantly decreased with a mismatched related donor (predominantly haploidentical; HR 0.62; $p < 0.001$) or almost for UD (HR 0.84; $p = 0.05$) resulting in improved LFS in the former (HR 0.80; $p = 0.04$) and improved GRFS in both types of alternative donor (mismatched related: HR 0.79; $p = 0.02$ and UD: HR 0.86; $p = 0.03$). OS and NRM were negatively affected by older age (HR 1.07; $p = 0.03$ and 1.18; $p = 0.003$, respectively, per 10-year increment).

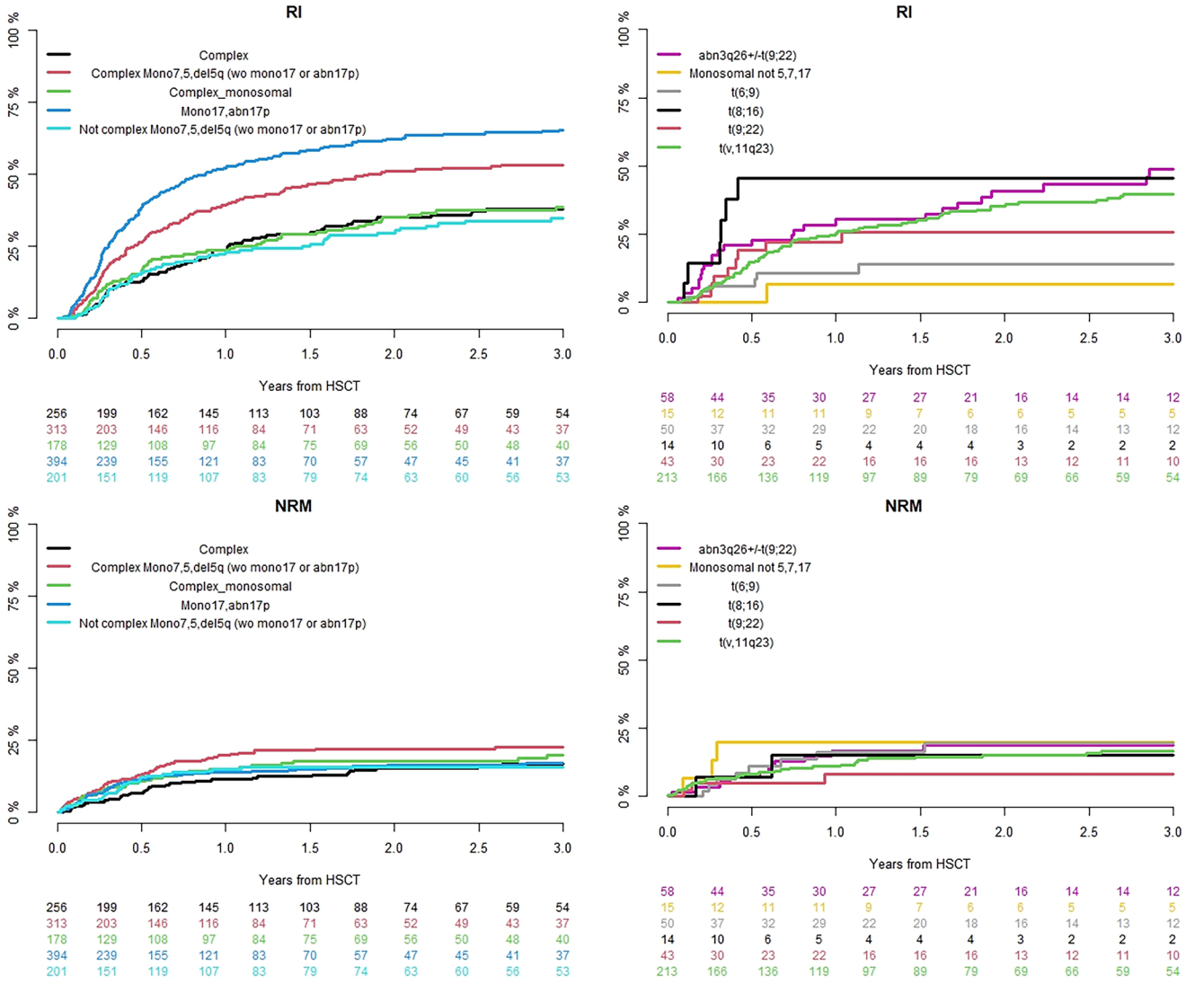

FIGURE 3 | Relapse incidence and non-relapse mortality according to cytogenetic subcategories. HSCT: hematopoietic stem cell transplant; NRM: non-relapse mortality; RI: relapse incidence.

4 | Discussion

This retrospective registry-based study provides a comprehensive analysis of the frequency and clinical impact of adverse cytogenetic abnormalities in a large number of AML patients ($n = 1735$) undergoing allo-HSCT in CR1. Our findings highlight the heterogeneity within these abnormalities, challenging the classification of CK and MK as universally adverse, particularly when chromosomes 5, 7, and 17 are not involved.

The adverse cytogenetic abnormalities were observed with variable frequency across the groups. Group 1 abnormalities, which involve monosomy 17/abn(17p), were the most frequent and highly associated with CK/MK and mutated *TP53*, followed by abnormalities in chromosomes 5 and 7 with CK. These groups demonstrated the poorest outcomes, with only 20% of patients achieving long-term survival post-transplant, similar to previous reports [15–17]. However, these findings reinforce the curative potential of allo-HSCT in this subset, albeit small. On the other hand, patients with chromosome 5 and 7 abnormalities without CK and/or abn(17p), which are classified as the third group by frequency, had relatively favorable outcomes, with long-term LFS achieved in 55% of patients. Similar findings were previously reported in a smaller study by the ALWP studying the prognosis of -5/5q- with or without other cytogenetic abnormalities in patients transplanted in CR1 [18]. The 5q sole group, which contained 47 patients, had a 2-year LFS and OS of 39% and 60%, respectively, significantly better than other groups including the CK group (25% and 31%), MK group (20% and 6%), and abn(17p) group (12% and 16%) [18].

Surprisingly, patients with CK showed relatively better outcomes when abnormalities in chromosomes 5, 7, and 17 were excluded. MK has consistently been classified as very poor in all reports, primarily due to the presence of monosomy 5, 7, or 17, which are strongly associated with poor survival, rather than other abnormalities [19–23]. Similar to our results, Middeke et al. demonstrated that the highly adverse prognostic significance of MK and CK in AML was mitigated after allo-HSCT, particularly when cases with abn(17p) or −5/del(5q) were excluded from these subcategories [24].

TABLE 3 | Multivariable analysis of outcomes.[a]

		LFS		OS		RI		NRM		GRFS	
Variables	**Modalities**	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Karyotype	Complex	1		1		1		1		1	
	Complex_ monosomal	1.14 (0.86–1.49)	0.36	1.21 (0.9–1.62)	0.2	1.08 (0.77–1.51)	0.67	1.29 (0.8–2.07)	0.29	1.17 (0.91–1.5)	0.22
	Mono17,abn17p	2.21 (1.78–2.74)	**<0.001**	2.41 (1.9–3.04)	**<0.001**	2.65 (2.05–3.44)	**<0.001**	1.39 (0.92–2.11)	0.12	2.05 (1.68–2.52)	**<0.001**
	Complex Mono7,5,del5q (wo mono17 or abn17p)	1.77 (1.41–2.23)	**<0.001**	1.86 (1.46–2.38)	**<0.001**	1.81 (1.37–2.39)	**<0.001**	1.73 (1.15–2.60)	**0.008**	1.66 (1.34–2.05)	**<0.001**
	Not complex Mono7,5,del5q (wo mono17 or abn17p)	0.88 (0.66–1.16)	0.36	0.83 (0.61–1.14)	0.25	0.9 (0.64–1.26)	0.54	0.83 (0.5–1.38)	0.47	0.95 (0.73–1.22)	0.67
	t(8;16)	2.02 (1.02–4.02)	**0.04**	2.81 (1.41–5.61)	**0.003**	1.78 (0.76–4.15)	0.18	2.94 (0.89–9.66)	0.08	1.54 (0.78–3.03)	0.21
	adv3q26+/−t(9;22)	1.31 (0.89–1.92)	0.17	1.2 (0.79–1.85)	0.4	1.45 (0.92–2.29)	0.1	1.05 (0.5–2.18)	0.9	1.32 (0.93–1.87)	0.12
	t(v,11q23)	1.01 (0.77–1.32)	0.97	1.04 (0.77–1.39)	0.81	1.04 (0.76–1.44)	0.8	0.97 (0.59–1.6)	0.91	0.93 (0.72–1.19)	0.57
	Monosomal not 5,7,17	0.68 (0.28–1.67)	0.4	0.84 (0.34–2.07)	0.7	0.21 (0.03–1.49)	0.12	1.60 (0.56–4.55)	0.38	1.36 (0.71–2.59)	0.35
	t(6;9)	0.63 (0.37–1.08)	0.09	0.71 (0.4–1.26)	0.24	0.44 (0.2–0.95)	**0.04**	1.1 (0.51–2.37)	0.81	0.84 (0.54–1.32)	0.45
	t(9;22)	0.57 (0.31–1.06)	0.08	0.43 (0.2–0.93)	**0.03**	0.6 (0.29–1.26)	0.18	0.52 (0.16–1.69)	0.28	0.58 (0.33–1.01)	0.05
Age at HSCT (effect for 10 years increment)		1.04 (0.99–1.10)	0.13	1.07 (1.01–1.14)	**0.03**	0.99 (0.93–1.06)	0.84	1.18 (1.06–1.31)	**0.003**	0.98 (0.93–1.03)	0.42
Year of HSCT		0.99 (0.97–1.01)	0.26	0.99 (0.97–1.01)	0.46	0.98 (0.96–1.01)	0.26	0.99 (0.95–1.03)	0.74	0.99 (0.97–1.01)	0.21
Type of AML	De novo	1		1		1		1		1	
	secAML	1.09 (0.95–1.26)	0.21	1.15 (0.99–1.33)	0.06	1.15 (0.97–1.36)	0.1	0.98 (0.75–1.27)	0.86	1.08 (0.95–1.23)	0.25

(Continues)

TABLE 3 | (Continued)

		LFS		OS		RI		NRM		GRFS	
Variables	**Modalities**	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Donor type	Matched related donor	1		1		1		1		1	
	Mismatched related donor	0.80 (0.64–0.99)	**0.04**.	0.89 (0.71–1.12)	0.31	0.62 (0.47–0.81)	**< 0.001**	1.38 (0.94–2.03)	0.1	0.79 (0.64–0.96)	**0.02**
	Unrelated donor	0.94 (0.81–1.09)	0.4	0.94 (0.8–1.1)	0.44	0.84 (0.71–1.01)	0.05	1.22 (0.9–1.65)	0.19	0.86 (0.75–0.99)	**0.03**
Myeloablative regimen	No	1		1		1		1		1	
	Yes	0.97 (0.84–1.12)	0.68	0.96 (0.83–1.12)	0.64	0.94 (0.79–1.12)	0.49	1.06 (0.81–1.39)	0.65	0.99 (0.87–1.13)	0.89
KPS	< 90	1		1		1		1		1	
	≥ 90	0.96 (0.83–1.10)	0.53	0.91 (0.78–1.05)	0.19	0.98 (0.82–1.17)	0.85	0.85 (0.66–1.09)	0.2	0.95 (0.83–1.08)	0.45

Note: Bold values indicate statistically significant *p*-values.

Abbreviations: abn: abnormal; AML: acute myeloid leukemia; CI: confidence interval; GRFS: graft-versus-host and relapse-free survival; HR: Hazard ratio; HSCT: Hematopoietic stem cell transplant; KPS: Karnofsky performance score; LFS: leukemia-free survival; mono: monosomy; NRM: non-relapse mortality; OS: overall survival; RI: relapse incidence; sec: secondary. *Note:* Bold values indicate statistically significant *p*-values.

[a]Centre effect or frailty was included in the models.

We have also examined the outcomes of other relatively rare entities, such as abn(3q26) and t(8;16), which are associated with intermediate post-transplant survival rates (2-year OS: 51% and 40%, respectively). These two groups represent distinct entities with more favorable outcomes compared to those with higher risk cytogenetic features, as approximately 40% of patients with these abnormalities achieved long-term disease control. Our findings demonstrate outcomes surpassing previously reported 2-year LFS and OS rates of 24% and 35%, respectively [25]. Of course, our cohort might represent a highly selected patient population with chemo-sensitive disease, transplanted in CR1, and is therefore not representative of the whole cohort of these entities at diagnosis. In addition, patients with BCR-ABL1-positive AML exhibited favorable survival outcomes, possibly highlighting the beneficial effects of allo-HSCT with peri-transplant use of tyrosine kinase inhibitors. Our results appear to surpass those previously reported, with a 2-year LFS of 66% compared to 47% in the earlier study [26, 27].

Interestingly, haploidentical and UD transplants demonstrated better outcomes compared to MSD grafts in this high-risk population. Unlike prior published studies, which did not report any difference based on donor type, these findings may be linked to enhanced graft-versus-leukemia effects associated with haploidentical or UD grafts, or the use of PTCy post-transplant, warranting further investigation into optimizing donor selection strategies for these patients with adverse cytogenetics.

One of the major limitations of this study is the reliance on patients with a complete cytogenetic report, which was essential for conducting the proposed analysis. Another limitation was the *TP53* mutation status unavailable for 81% of cases, limiting the ability to perform further analysis regarding the likelihood of overlap between the poor cytogenetic profiles and *TP53*-mutated AML, as well as its potential contribution to the poor post-transplant outcomes observed.

In conclusion, this large real-world study revealed a very poor outcome of allografted AML patients with monosomy 17 or 17p abnormalities and CK involving monosomy 5, monosomy 7, del5q, and a poor outcome for those with abn(3q26) and t(8;16). Importantly, our findings suggest that the presence of either 17p abnormalities or the combination of CK with monosomy 5 or 7 is necessary to define the subset of patients with the worst prognosis. Within the ELN-2022 adverse risk population, patients with CK alone or monosomy 5 or 7 alone exhibited relatively favorable post-transplant outcomes.

Ethics Statement

The data analyzed in this study were provided and approved by the ALWP of the EBMT. Since January 2003, all transplant centers have been required to obtain written informed consent prior to data registration with the EBMT, following the guidelines of the Declaration of Helsinki, 1975.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All relevant data are provided within the Article and the Supporting Information. The relevant working party of the EBMT will review requests from qualified external researchers for data from the EBMT studies in a responsible manner that includes protecting patient privacy, assurance of data security and integrity, and furthering scientific and medical innovation. Additional details on data sharing criteria and process for requesting access should be sent to ebmt.do-paris@ebmt.org. Individual patient data will not be shared.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.