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Letter to the Editor

Differences in the clinical and genetic profile of Hispanic and non-Hispanic acute myeloid leukemia patients

To the Editor,

The role of Hispanic ethnicity in leukemia occurrence and outcome has been studied with mixed results. Acquired cytogenetic abnormalities and genetic mutations are powerful prognostic tools to predict survival in acute myeloid leukemia (AML) patients [1]. Hispanic AML patients were found to have more frequent high-risk mutations and poorer survival than non-Hispanics [2], and an excess risk of death despite younger age at diagnosis and a more favorable karyotype profile [3]. Mortality disparities between minority and White AML patients may be driven by adverse mutations acquired through environmental or occupational exposures, as well as differences in receipt of chemotherapy and hematopoietic stem cell transplantation [4]. Genetic prognostic markers recommended by the European Leukemia Net (ELN) have been successfully used to predict patient's clinical outcomes among AML patients in low and middle-income countries (LMIC) [5]. A study on 196 Brazilian AML patients reported lower survival rates compared to high-income countries, even among patients with favorable cytogenetics, possibly due to lack of hospital infrastructure, higher risk of infection, and other disadvantages [5]. To date, the inter-relationship between Hispanic ethnicity, cytogenetics, and treatment factors has not been adequately evaluated in AML patients in a developed country like the United States, and particularly acute promyelocytic leukemia (APL) patients.

To address this gap, we retrospectively analyzed data from a hospital-based clinical registry, with the objective of describing ethnic differences among a clinical cohort of AML patients in terms of demographics, risk factors, cancer and treatment history, cytogenetics, and genetic mutations.

The clinical cohort comprised 390 inpatients and outpatients diagnosed with AML, cared for at the Mount Sinai Health System, New York, from 1/1/2009-12/31/2016. Cases were electronically and manually identified from within Mount Sinai's Data Warehouse, a collection of clinical, financial and operational data from over 20 sources at the Mount Sinai Hospital and Mount Sinai Faculty Practice Associates. Variables extracted included demographics, cancer-related factors (AML type, history of solid tumor, hematological disorder and prior chemotherapy), and molecular and cytogenetic information (available for 256 patients at diagnosis). AML was classified as "de novo" and "secondary" (secondary to myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), or therapy related). Genetic mutations were identified using a next-generation sequencing (NGS) panel. The entire coding region was sequenced for the genes assessed. Patients carrying at least one of the following acquired gene mutations: *ASXL1, FLT3, DNMT3A, RUNX1, TET2, TP53, PHF6* were classified as having a deleterious mutation, as they are associated with AML and poor prognosis; mutations indicative of favorable prognosis (including *NPM1* and *CEBPA*) were also identified [1]. Patients were classified as having an abnormal karyotype if any structural or numerical chromosomal abnormality was present in ≥ 2 cells (≥ 3 cells for monosomy) [6]. Three or more distinct chromosomal abnormalities in the same patient were considered a "complex" karyotype [7]. Exposure signature was defined as a patient's genetic profile suggestive of past exposure to commonly known mutagens [8]. Karyotype abnormalities were further classified as "favorable" or "unfavorable" (intermediate I/ II, adverse), using the European Leukemia Net (ELN) guidelines [9]. This study was approved by the Institutional Review Board at Mount Sinai Hospital (Protocol #IRB1701298). Since the data were de-identified and retrospectively collected, informed consent was waiver for this study. All protected health information was kept confidential on institutional servers accessible through password-protected computers.

Statistical analyses were conducted using SAS analytic software. Demographic characteristics were assessed for the cohort (N = 390). Logistic regression models assessed the association between ethnicity (Hispanic vs non-Hispanic) and AML characteristics, history of cancer and chemotherapy, and presence of favorable and deleterious mutations, adjusted for age category and presented as Odds Ratios (OR) and 95% confidence intervals (CI). Frequencies of individual deleterious and favorable mutations were compared according to Hispanic ethnicity using chi-square or Fisher's exact tests, and p-values for significance are presented. Results were stratified by APL status where applicable. Risk of death by Hispanic ethnicity was assessed using Cox proportional hazards regression, was stratified by specific clinical characteristics and results are presented as Hazard Ratios (HR) and 95% CI. All statistical tests were conducted at significance level $\alpha = 0.05$.

The study sample had a median age of 62 years and consisted of 52% males, 53% Whites, 15% Blacks, and 32% other races. Ethnically, about 20% were Hispanic. There were no statistically significant differences between Hispanics and non-Hispanic patients in terms of age, gender, non-White race, alcohol or tobacco use. Hispanics with AML were significantly less likely than non-Hispanics to have secondary AML (25% vs 41%; Adjusted odds ratio (AOR) = 0.48;95%CI = 0.26-0.88) and history of antecedent hematological disease (19% vs 35%;AOR = 0.45;95%CI = 0.23-0.87) (Table 1). Hispanic ethnicity was positively, although non- significantly, associated with having APL (10% vs 8%; AOR = 1.22; 95%CI = 0.42–3.17), a complex karyotype (45% vs 30%; AOR = 2.01;95%CI = 0.74–5.41), and a higher percentage of bone marrow blasts than non-Hispanics (59% vs 52%;p > .05). Although there was no overall difference in presence of genetic mutations (deleterious and total), Hispanics had a significantly higher frequency of *TP53* mutation (11% vs 2%; p = 0.03), and a non-statistically significant higher frequency of *RUNX1* mutation (8% vs 4%; p = 0.38). Most associations were similar in magnitude and direction for non-APL patients. Among APL patients, Hispanics were more likely to be younger (below the median age of 63 years) and male compared to non-Hispanics. No significant ethnic differences in exposure signature,

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Table 1
Association of AML characteristics and cytogenetics with Hispanic ethnicity, according to histologic type.

Characteristics	AML (n = 390)			APL[1] (n = 31)[4]			Non-APL[1] (n = 343)		
	N (%)		OR_{adj} (95%CI)[2]	N (%)		OR_{adj} (95%CI)[2]	N (%)		OR_{adj} (95%CI)[2]
	Hispanic N = 70	Non-Hispanic (ref) N = 286		Hispanic N = 7	Non-Hispanic (ref) N = 23		Hispanic N = 60	Non-Hispanic (ref) N = 252	
Age ≥63 years	30 (43)	134 (47)	0.85 (0.50, 1.44)	1 (14)	6 (26)	0.48 (0.01, 5.50)	28 (47)	125 (50)	0.89 (0.51, 1.56)
Male gender	36 (51)	145 (51)	1.04 (0.62, 1.76)	4 (57)	11 (48)	1.27 (0.16, 10.8)	31 (52)	126 (50)	1.08 (0.61, 1.90)
Non-white race	35 (50)	131 (46)	1.16 (0.68, 1.97)	2 (29)	12 (52)	0.33 (0.03, 2.63)	32 (53)	115 (46)	1.35 (0.76, 2.38)
Prior solid tumor	9 (13)	49 (18)	0.74 (0.34, 1.62)	0 (0)	4 (18)	0.63 (0.00, 4.33)	8 (14)	44 (18)	0.75 (0.33, 1.72)
Prior hematological disorder	13 (19)	98 (35)	0.45 (0.23, 0.87)	0 (0)	3 (14)	0.64 (0.00, 4.67)	13 (23)	92 (37)	0.51 (0.26, 1.00)
Prior cancer therapy	12 (18)	74 (27)	0.60 (0.30, 1.18)	0 (0)	5 (23)	0.46 (0.00, 2.87)	11 (19)	69 (28)	0.61 (0.30, 1.24)
APL[1]	7 (10)	23 (8)	1.22 (0.42, 3.17)						
Secondary AML	17 (25)	115 (41)	0.48 (0.26, 0.88)	0 (0)	3 (14)	1.06[5]	16 (27)	110 (44)	0.47 (0.25, 0.88)
Abnormal karyotype present	33 (65)	118 (65)	1.00 (0.52, 1.91)	3 (100)	12 (100)	N/A[9]	28 (61)	105 (64)	0.90 (0.46, 1.76)
Unfavorable ELN category[3,8]	16 (67)	70 (82)	0.41 (0.15, 1.18)	N/A	N/A	N/A	16 (73)	69 (87)	0.38 (0.12, 1.25)
Exposure signature present[3]	9 (47)	33 (59)	0.67 (0.23, 1.97)	0 (0)	1 (25)	4.00[5]	8 (47)	32 (62)	0.59 (0.19, 1.82)
Complex karyotype present[3]	10 (45)	22 (30)	2.01 (0.74, 5.41)	0 (0)	0 (0)	Not estimable	9 (47)	22 (33)	1.99 (0.70, 5.66)
At least one mutation present	21 (34)	91 (35)	0.93 (0.51, 1.67)	1 (17)	5 (23)	0.65 (0.01, 8.03)	20 (37)	81 (36)	1.06 (0.57, 1.96)
At least one deleterious mutation	13 (21)	59 (23)	0.88 (0.45, 1.75)	1 (17)	5 (23)	0.65 (0.01, 8.03)	12 (22)	52 (23)	0.96 (0.47, 1.96)
Specific deleterious mutations	**N (%)**		**p-value**[10]	**N (%)**		**p-value**[10]	**N (%)**		**p-value**[10]
ASXL1	1 (2.7)	4 (2.7)	1.000	0 (0.0)	0 (0.0)	–	1 (2.9)	4 (3.0)	1.000
FLT3	8 (21.6)	35 (23.2)	0.840	1 (100)	4 (33.3)	0.385	7 (20.6)	30 (22.6)	0.805
DNMT3A	2 (5.4)	13 (8.6)	0.739	0 (0.0)	1 (8.3)	1.000	2 (5.9)	11 (8.3)	1.000
RUNX1	3 (8.1)	6 (4.0)	0.383	0 (0.0)	0 (0.0)	–	3 (8.8)	6 (4.5)	0.390
TET2	2 (5.4)	13 (8.6)	0.739	0 (0.0)	0 (0.0)	–	2 (5.9)	13 (9.8)	0.738
TP53	4 (10.8)	3 (1.9)	0.029	0 (0.0)	0 (0.0)	–	4 (11.8)	3 (2.3)	0.032
PHF6	0 (0.0)	1 (0.7)	1.000	0 (0.0)	0 (0.0)	–	0 (0.0)	1 (0.8)	1.000
Specific favorable mutations									
NPM1	7 (10.0)	33 (11.5)	0.696)	0 (0.0)	0 (0.0)	–	7 (11.7)	29 (11.5)	0.877
CEBPA	0 (0.0)	8 (2.8)	0.359)	0 (0.0)	0 (0.0)	–	0 (0.0)	8 (3.2)	0.361
	μ (SE)[6]		**β_{adj} (95%CI)**[7]	**μ (SE)**[6]		**β_{adj} (95%CI)**[7]	**μ (SE)**[6]		**β_{adj} (95%CI)**[7]
Percentage of bone marrow blasts at diagnosis	59 (3.7)	52 (1.8)	7.3 (-0.6, 15.3)	89 (11.4)	71 (6)	17.4 (-8.0, 42.7)	56 (3.8)	49 (1.9)	6.1 (-2.3, 14.4)

Note: APL/non-APL status was known for 374 patients.
[1] APL = Acute promyelocytic leukemia.
[2] Odds Ratio (95% Confidence interval) comparing Hispanics to non-Hispanics (age-adjusted, except for age category).
[3] Calculated for patients with abnormal karyotype.
[4] Exact conditional logistic regression performed due to very low numbers in strata.
[5] CI not estimable.
[6] μ = Least square mean; SE = standard error of the mean.
[7] β = Mean difference; CI = confidence interval.
[8] ELN cytogenetic risk categories are not used for APL, hence marked N/A (not applicable).
[9] All APL patients have abnormal karyotype, hence marked N/A.
[10] P-values reported for χ^2 test of association; Fisher's exact test performed where expected cell counts were < 5.

complexity or genetic mutations were found among APL patients.

Overall, Hispanics did not have a significantly higher risk of death than non-Hispanics after adjusting for age, gender, and prior chemotherapy (Table 2). Compared to non-Hispanics, risk of death was non-significantly higher among Hispanics with secondary AML (AHR = 1.43; 95%CI = 0.78–2.6), and with prior chemotherapy (AHR = 1.48;95%CI = 0.75–2.92). Among patients with *TP53* mutations, Hispanics had non-significantly higher unadjusted risk of death compared with non-Hispanics (HR = 2.91; 95%CI = 0.41–20.9); similarly among patients with *RUNX1* mutations (HR = 2.54; 95%CI = 0.26–24.6).

These results, although not statistically significant, uphold previous reports that Hispanics are more likely to have APL compared to non-Hispanic AML patients. A large retrospective study on 1018 acute leukemia patients across 5 Mexican states found that APL was the most common histological subtype, comprising 35% of AML patients (177/499) [10]. They suggested that high prevalence of overweight/obesity in Mexico may increase APL risk among Latinos. They further attributed the relatively younger age of their AML cohort to the older demographics of developed countries as well as lower diagnostic accuracy in elderly patients in developing countries due to lack of access. Our study also adds to existing evidence that secondary and chemotherapy-associated AML have a poor prognosis [11]. The novel finding that one specific p53 mutation (*TP53,* OMIM #191,117) was significantly more frequent among Hispanics than non-Hispanics (fivefold) needs to be corroborated by additional research. Darbinyan et al. [2] had found a similar association, but the result was not statistically significant. Exposure to specific environmental mutagens leaves characteristic signatures ("fingerprints") on the *TP53* gene, which have been linked to cancer occurrence [12]. Higher overall cancer risk in Hispanics compared to Whites has been previously attributed to certain indoor hazardous chemicals like p-DCB, chloroform, and benzene [13]. Reported spatial and temporal clustering of APL suggests a role of specific environmental and/or occupational exposures [14,15]. Degree of acculturation may also determine environmental exposures, since foreign-born Hispanics were found to have a higher APL incidence rate versus US-born Hispanics [16]. *TP53* mutation is a well-known prognostic factor associated with low AML survival rates, particularly among those with complex karyotype [17]. In this study, Hispanics were more likely to have complex karyotype; moreover, among patients with complex karyotype, *TP53* mutations were more prevalent among Hispanics (50%) than non-Hispanics (11%). *TP53* mutations are also currently a focus of anti-cancer drug development [18] and may inform targeted treatment options based on patient mutational profile.

RUNX1 mutations were twice as common among Hispanics, similar to reports by Darbinyan et al. [2]. Combined with noncomplex

Table 2
Risk of death in Hispanic compared with non-Hispanic AML patients.

Subgroups	N (%)[1]		Median survival (days)[1]		Hazard ratio for Hispanics vs non-Hispanics (95% confidence interval)	
	Hispanic	Non-Hispanic	Hispanic	Non-Hispanic	Unadjusted model	Adjusted model[2]
All participants	67 (19.6)	274 (80.4)	309	277	0.84 (0.59, 1.22)	0.88 (0.60, 1.28)
By gender						
Male	36 (51.4)	145 (50.7)	275	269	0.76 (0.46, 1.27)	0.77 (0.44, 1.33)
Female	34 (48.6)	141 (49.3)	309	292	0.93 (0.55, 1.58)	1.01 (0.59, 1.71)
Age category, years (quartiles)						
> 73	17 (25.4)	65 (23.6)	119	124	0.90 (0.49, 1.64)	0.90 (0.49, 1.67)
63–72	13 (19.4)	69 (25.1)	239	244	0.55 (0.22, 1.40)	0.69 (0.23, 2.04)
50–62	18 (26.9)	70 (25.5)	229	310	1.01 (0.50, 2.04)	1.05 (0.52, 1.71)
< 50	19 (28.4)	71 (25.8)	561	437	0.74 (0.31, 1.77)	0.69 (0.28, 1.69)
Type of AML						
Secondary to MDS/MPN/therapy	17 (24.6)	115 (40.9)	125	183	1.50 (0.85, 2.65)	1.43 (0.78, 2.60)
De novo	52 (75.4)	166 (59.1)	459	363	0.76 (0.47, 1.25)	0.69 (0.42, 1.13)
ELN category						
Unfavorable (Adverse/intermediate)	16 (66.7)	70 (82.4)	82	126	0.96 (0.47, 1.97)	1.35 (0.64, 2.87)
Favorable	8 (33.3)	15 (17.7)	486	514	0.98 (0.18, 5.33)	1.75 (0.21, 14.34)
Complex karyotype						
Yes	10 (45.5)	22 (30.1)	53	74	0.94 (0.39, 2.25)	1.03 (0.39, 2.72)
No	12 (54.6)	51 (69.9)	486	183	0.24 (0.06, 1.02)	0.29 (0.07, 1.28)
Prior cancer therapy						
Yes	56 (82.4)	204 (73.4)	119	166	1.47 (0.77, 2.80)	1.48 (0.75, 2.92)
No	12 (17.7)	74 (26.6)	379	320	0.76 (0.48, 1.19)	0.69 (0.44, 1.09)
TP53 mutation[2]						
Present	4 (10.8)	3 (1.9)	69	212	2.91 (0.41, 20.99)	Not estimable
Absent	33 (89.2)	148 (98.0)	321	337	0.91 (0.52, 1.58)	0.93 (0.53, 1.63)
RUNX1 mutation[2]						
Present	3 (8.1)	6 (4.0)	111	385	2.54 (0.26, 24.61)	Not estimable
Absent	34 (91.9)	145 (96.0)	328	320	0.86 (0.49, 1.53)	0.88 (0.49, 1.58)
NPM1 mutation[2]						
Present	7 (19.4)	32 (21.8)	194	277	1.19 (0.39, 3.64)	1.11 (0.33, 3.67)
Absent	29 (80.6)	115 (78.2)	310	277	0.78 (0.53, 1.16)	0.92 (0.62, 1.38)

[1] Reported among patients with complete data on follow-up time, ethnicity, and mutational information (for gene mutations).
[2] Adjusted for age category, gender, prior cancer therapy (unless stratified by one of these variables).

karyotype AML, these mutations are associated with shorter survival [19]. *FLT3*-ITD mutations occurred somewhat more frequently in APL Hispanic patients; they may indicate an overall genetic instability, leading to accumulation of additional genetic and epigenetic events associated with poor prognosis [20].

This study has certain limitations. Clinical data were manually extracted from electronic medical records, and depended on documentation and data availability. Some referred patients received their initial care at an outside institution, leading to missing cytogenetic data. Full mutational profiling was not routine until later in the clinical cohort. It is thus possible that due to fewer patients with APL and missing mutational and karyotype information, certain meaningful associations went undetected. Due to data set limitations, it was not possible to assess the effect of socioeconomic variables such as insurance, income, education level, etc. on ethnic differences in AML outcomes. The study results should be interpreted in context of New York City, since the Hispanic population in other parts of the USA may originate from different countries and therefore may be genetically different.

Nevertheless, this is the first study to report a statistically significant association between Hispanic ethnicity and presence of a *TP53* mutation among AML patients. Ethnic differences in APL risk may be driven by a combination of cytogenetics, treatment history, and environmental risk factors. It is important to identify modifiable risk factors (including environmental and occupational) and devise strategies to eliminate disparities among Hispanic patients.

Conflict of interest

All authors declare no conflicts of interest for this manuscript, financial or otherwise.

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