Abstract MDS-556

Comparison of Demographics, Disease Characteristics and Outcomes Between African Americans and Whites With Myelodysplastic Syndrome: A Population-Based Study

Arnaud Lesegretain,[1,2] Abderrahmane Laadem,[2] Geoffrey Fell,[3] Amir T. Fathi[4]

[1]Harvard Medical School, Boston, MA, USA; [2]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]Massachusetts General Hospital, Boston, MA, USA

Please contact Arnaud Lesegretain at alesegretai@hms.harvard.edu if you have any questions or need additional information

Introduction

- Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal myeloid neoplasms characterized by morphologic dysplasia, ineffective hematopoiesis, progressive and refractory peripheral cytopenias, and risk of progression to acute myeloid leukemia (AML)
  - Overall, long-term survival outcomes are poor compared with other cancers (~29% 5-year overall survival [OS])
  - Clinical outcomes are highly variable, with some patients having close-to-normal life expectancy and others having very poor outcomes
  - The disease is very heterogenous and diagnosis is especially complex
- The classification of MDS both clinically and in population-based registries has changed significantly over the last decades, including changes to the International Classification of Diseases for Oncology (ICD-O), the French-American-British criteria (1976), and multiple iterations of the World Health Organization (WHO) classification (2001, 2008, and 2016)
- Disparities in cancer care and cancer outcomes between Black and White patients are well documented for some solid tumors and hematologic malignancies, including AML
- However, the association between race and outcomes remains poorly studied and controversial in MDS

Objectives

- We thought to characterize and compare baseline demographics, clinical characteristics, socioeconomic factors and OS for patients with MDS between Black and White populations. We also thought to characterize the most frequent causes of death (COD) overall and between Black and White cohorts

Methods

Population

- The Surveillance, Epidemiology, and End Results (SEER) Program collects cancer incidence, mortality, and COD data for ~28% of the United States population
- Analysis included MDS cases from the National Cancer Institute SEER registry using the SEER Research Plus database, 18 registries, and November 2020 submission (2000-2018)
  - Had to have microscopically confirmed MDS diagnosis per SEER between 2001 and 2013; cutoff date of December 2018
- Extracted cases had the following ICD-O version 3 (ICD-O-3) codes:
  - Refractory anemia (RA; 9980)
  - RA with ring sideroblasts (RARS; 9982)
  - RA with excess blasts (RAEB; 9983)
  - Refractory cytopenia with multilineage dysplasia (RCMD; 9985)
  - MDS associated with isolated del(5q) (9986)
  - MDS, unclassifiable (MDS-U; 9989); labeled MDS-NOS in our study to avoid confusion with WHO-defined MDS-U
  - Refractory neutropenia (RN; 9991)
  - Refractory thrombocytopenia (RT; 9992)
- ICD-O-3 subtypes of MDS were grouped, based on OS into lower risk (RA, RT, RN, RARS), intermediate risk (RCMD, MDS del(5q), MDS-NOS), and higher risk (RAEB) disease
- Inclusion criteria: ≥20 years of age at MDS diagnosis, MDS was the first cancer diagnosed in SEER
- Exclusion criteria: therapy-related MDS and MDS in-transformation, with zero days of follow-up or zero days of survival, and diagnosis based on autopsy or death certificate only
- This study was considered exempt by the Dana-Farber Harvard Cancer Institute Institutional Review Board

Statistical Analysis

- Chi-square analysis was used to compare baseline categorical covariates between races; Wilcoxon rank-sum was used to compare median age at diagnosis between races
- The Kaplan-Meier method was used to estimate OS; the log-rank test was used to compare between groups
- Multivariate Cox regression and matching analyses were conducted to reduce effects of confounding due to imbalances in baseline covariates between Black and White populations
- Analyses were performed using Stata 17.0 BE (StataCorp LLC, College Station, TX, USA); age-adjusted incidence was computed with SEER*Stat software (version 8.3.9.2)
- Statistical significance for all tests was declared for 2-sided p<0.05

Results

- A total of 37,562 patients with MDS were identified, with a median age of 76 years (interquartile range [IQR], 67-82 years; **Table 1**), of whom 81.1% were diagnosed after 65 years of age; 57.3% were male, 8.1% were Black, and 91.9% were White
  - There was a greater proportion of female patients among the Black cohort (50.8%) versus the White cohort (42.0%)
  - Median age was younger among Black patients (71 years; IQR, 61-79 years) versus White patients (76 years; IQR, 68-83 years)
  - More White patients (53.4%) than Black patients (36.7%) were married
  - A total of 66.9% of Black versus 60.3% of White patients lived in large metropolitan areas
  - More Black patients (80.6%) than White patients (67.4%) lived in counties with lower median household income (<75,000 United States dollars/year)

Table 1. Patient Demographics

	All patients with MDS		Black patients		White patients		
	N	%	N	%	N	%	p value
	37,562	100.0	3037	8.1	34,525	91.9	
Sex							<0.001
Male	21,515	57.3	1495	49.2	20,020	58.0	
Female	16,047	42.7	1542	50.8	14,505	42.0	
Median (IQR) age, years	76 (67-82)		71 (61-79)		76 (68-83)		<0.001
Age group, years							<0.001
20-44	834	2.2	165	5.4	669	1.9	
45-54	1711	4.6	258	8.5	1453	4.2	
55-64	4559	12.1	555	18.3	4004	11.6	
65-74	9622	25.6	849	28.0	8773	25.4	
75-84	14,301	38.1	850	28.0	13,451	39.0	
85+	6535	17.4	360	11.9	6175	17.9	
Marital status							<0.001
Single	3288	8.8	581	19.1	2707	7.8	
Married	19,536	52.0	1116	36.7	18,420	53.4	
Separated/divorced/widowed	11,139	29.7	1064	35.0	10,075	29.2	
Other/unknown	3599	9.6	276	9.1	3323	9.6	
Metropolitan status							<0.001
Large metropolitan area (>1 million)	22,836	60.8	2031	66.9	20,805	60.3	
Small metropolitan area (≤1 million)	10,078	26.8	694	22.9	9384	27.2	
Nonmetropolitan area	4648	12.4	312	10.3	4336	12.6	
Income bracket, USD							<0.001
<75,000	25,735	68.5	2448	80.6	23,287	67.4	
≥75,000	11,781	31.4	584	19.2	11,197	32.4	

IQR, interquartile range; MDS, myelodysplastic syndrome; USD, United States dollars.

- The proportions of Black patients with RA, RAEB, and MDS-NOS were 14.2%, 14.6%, and 53.9%, respectively, compared with 11.7%, 16.3%, and 51.8%, respectively, for White patients (**Table 2**)
- Age-adjusted incidence rate was 5.8/100,000 for Black patients versus 7.0/100,000 for White patients (**Table 3**)

Table 2. Disease Characteristics

	All patients with MDS		Black patients		White patients		
	N	%	N	%	N	%	p value
	37,562	100.0	3037	8.1	34,525	91.9	
Histology							<0.001
RA	4461	11.9	431	14.2	4030	11.7	
RARS	3669	9.8	268	8.8	3401	9.9	
RAEB	6077	16.2	442	14.6	5635	16.3	
RCMD	2693	7.2	198	6.5	2495	7.2	
MDS del(5q)	1148	3.1	61	2.0	1087	3.1	
MDS-NOS	19,514	52.0	1637	53.9	17,877	51.8	
Prognostic risk group							0.016
Low	8130	21.6	699	23.0	7431	21.5	
Intermediate	23,355	62.2	1896	62.4	21,459	62.2	
High	6077	16.2	442	14.6	5635	16.3	
Year of diagnosis							0.17
2000-2004	9554	25.4	804	26.5	8750	25.3	
2005-2013	28,008	74.6	2233	73.5	25,775	74.7	

MDS, myelodysplastic syndrome; MDS del(5q), myelodysplastic syndrome associated with isolated del(5q); MDS-U, myelodysplastic syndrome, unclassifiable; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ring sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia.

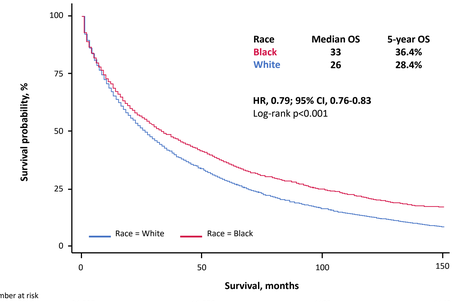
Table 3. Age-Adjusted Incidence by Histology Between 2001 and 2013 for adult MDS patients

	Black patients			White patients		
	Rate	95% CI		Rate	95% CI	
Overall	5.8[a]	5.6	6.0	7.0	6.9	7.0
RA	0.8	0.7	0.8	0.8	0.7	0.8
RARS	0.4[a]	0.4	0.5	0.6	0.6	0.6
RAEB	0.7[a]	0.6	0.7	0.9	0.9	1.0
RCMD	0.3[a]	0.3	0.3	0.4	0.4	0.4
MDS del(5q)	0.1[a]	0.1	0.1	0.2	0.2	0.2
MDS-NOS	3.5[a]	3.3	3.6	4.1	4.0	4.1

Age-adjusted to the 2000 US standard population (19 age groups: Census P25-1130) standard; CIs (Tiwari modification) are 95% for rates. Rates are per 100,000.
MDS del(5q), myelodysplastic syndrome associated with isolated del(5q); MDS-U, myelodysplastic syndrome, unclassifiable; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ring sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; US, United States.
[a]Rate ratio (not shown) for Black patients is statistically different from White patients.

- In univariate analysis, there was a statistically significant association between race and OS in favor of Black patients (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.76-0.83; p<0.001; **Figure 1**)
  - Median OS (mOS): 33 months versus 26 months for Black versus White patients

Figure 1. Overall Survival



Number at risk

Race = White	34,525	11,556	4185	1142
Race = Black	3037	1249	540	195

CI, confidence interval; HR, hazard ratio; OS, overall survival.

- When adjusting for baseline covariates in multivariate Cox proportional hazards regression models, association between race and survival remained statistically significant (**Table 5**)

Table 4. Association of Race and Overall Survival for Patients With MDS From Cox Regression Models (N=37,562)

		Outcome: overall survival					
		3-year follow-up			5-year follow-up		
		Events	HR (95% CI)	p value[a]	Events	HR (95% CI)	p value[b]
Black vs White	Unadjusted	21,805	0.84 (0.80-0.89)	<0.001	26,578	0.83 (0.79-0.86)	<0.001
	Adjusted[b,c]	21,805	0.92 (0.88-0.97)	0.003	26,578	0.92 (0.88-0.96)	<0.001

CI, confidence interval; HR, hazard ratio; MDS, myelodysplastic syndrome; OS, overall survival.
[a]Multivariable model controlled for the following variables: sex, age group, MDS histology, marital status, metropolitan residential status, income group, and year of diagnosis.
[b]p values are from Cox proportional hazard regression model. An HR <1 (>1) corresponds to a lower (higher) value for the first level of listed dichotomous variable.
[c]Statistically significant interaction was detected between race-OS and histology (Chi-square=11.25; DF=5; p=0.045) and residential status (Chi-square=10.43; DF=2; p=0.005).

- There was an interaction between the association of race and survival with histology (p=0.045) and with urban-rural code (p=0.005), which indicate that the association between race and survival varied significantly across different values of patient histology and patient location on the urban-rural continuum code

Table 5. Subgroup Analysis of the Multivariable[a] Cox Regression Model of the Association of Race and Overall Survival by MDS Histology According to SEER (N=37,562)

	Patients, N	Frequency, %	Events, N	HR[b] (95% CI)	p value[c]
RA	4461	11.9	2699	0.87 (0.76-1.00)	0.05
RARS	3669	9.8	2061	1.12 (0.95-1.32)	0.18
RAEB	6077	16.2	5494	1.04 (0.94-1.16)	0.42
RCMD	2693	7.2	1956	0.87 (0.73-1.05)	0.16
MDS del(5q)	1148	3.1	821	1.30 (0.96-1.76)	0.09
MDS-NOS	19,514	52.0	13,547	0.90 (0.85-0.97)	0.003

CI, confidence interval; HR, hazard ratio; MDS, myelodysplastic syndrome; MDS del(5q), myelodysplastic syndrome associated with isolated del(5q); RA, refractory anemia; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ring sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; SEER, Surveillance, Epidemiology, and End Results.
[a]Multivariable model controlled for the following variables: sex, age group, marital status, metropolitan residential status, income group, and year of diagnosis.
[b]An HR <1 (>1) corresponds to a lower (higher) value for Black compared with White patients with MDS.
[c]p values are from Cox proportional hazard regression model with a 5-year follow-up.

- We observed heterogeneity between MDS subsets, with 3 subsets having a point estimate for the HR of OS >1 and 3 subsets with a point estimate <1
- MDS-NOS, which represents 52% of the cases in our study, was the only histology subset with a statistically significant association (HR [95% CI], 0.90 [0.85-0.97]; p=0.003)
- We observed a consistent effect in favor of Black patients for the populations living in large, small, and nonmetropolitan areas with point estimates all <1 (**Table 6**). The strongest (and only statistically significant) association was detected for patients living in nonmetropolitan areas

Table 6. Analysis of the Multivariable[a] Cox Regression Model of the Association of Race and Overall Survival by Metropolitan Residential Status According to SEER (N=37,562)

	Patients, N	Frequency, %	Events, N	HR[b] (95% CI)	p value[c]
Large metropolitan area (>1 million)	22,836	60.8	15,994	0.95 (0.90-1.01)	0.114
Small metropolitan area (≤1 million)	10,078	26.8	7268	0.92 (0.83-1.01)	0.081
Nonmetropolitan area	4648	12.4	3316	0.75 (0.64-0.87)	0.001

CI, confidence interval; HR, hazard ratio; MDS, myelodysplastic syndrome; SEER, Surveillance, Epidemiology, and End Results.
[a]Multivariable model controlled for the following variables: sex, age group, marital status, metropolitan residential status, income group, and year of diagnosis.
[b]An HR <1 (>1) corresponds to a lower (higher) value for Black compared with White patients with MDS.
[c]p values are from Cox proportional hazard regression model with a 5-year follow-up.

- The percentage of MDS-NOS has been relatively stable over time in SEER, ranging from 48.1% to 54.6% over the study period (not shown)
- However, we observed large variability in the proportion of MDS-NOS in the various regional cancer registries included in SEER, ranging from 31.8% in Seattle to 60.1% in New Jersey. We also observed variability in the percentage of White and Black patients among MDS-NOS (**Table 7**)

Table 7. Information on MDS-NOS Subset in Each Regional Cancer Registry

	Entire study population		MDS-NOS subgroup		
Registry	MDS cases	MDS-NOS, %	White, %	Black, %	Difference, %
California	13,239	55.8	55.8	56.0	0.2
Connecticut	1912	58.5	58.7	55.3	-3.4
Georgia	3476	58.1	57.4	61.5	4.1
Hawaii	158	41.8	42.3	0.0	-42.3
Iowa	2128	45.2	45.3	27.8	-17.5
Kentucky	2004	50.0	49.9	51.5	1.6
Louisiana	2224	40.1	40.5	38.4	-2.1
Detroit	2836	44.1	43.6	46.3	2.7
New Jersey	5428	60.1	59.6	65.3	5.7
New Mexico	697	50.6	50.8	37.5	-13.3
Utah	824	44.5	44.6	25.0	-19.6
Seattle	2636	31.8	31.7	37.7	6.0
Total	**37,562**	**52.0**	**51.8**	**53.9**	**2.1**

MDS, myelodysplastic syndrome.

- MDS/leukemia, cardiovascular disease (CVD), and other malignancies were the 3 most frequent COD in both Black and White patients (**Table 8**)
- Death attributed to MDS/leukemia represented the most frequent COD overall (46.6%) and was higher for White patients (47.2%) compared with Black patients (39.3%)
- Death attributed to CVD was the second most common overall (18.0%) and was more common among Black versus White patients (19.6% vs 17.8%)
- The third most frequent COD was that due to other malignancies (10.9%) and was 12.4% for Black patients and 10.8% for White patients

Table 8. Vital Status and Frequency of Attributed COD

	All patients with MDS		Black		White		
	N	%	N	%	N	%	p value[a]
Vital status at study cutoff							<0.001
Alive	5049	13.4	638	21.0	4411	12.8	
Dead	32,513	86.6	2399	79.0	30,114	87.2	
COD[b]							<0.001
MDS/leukemia	15,154	46.6	944	39.3	14,210	47.2	
CVD	5841	18.0	470	19.6	5371	17.8	
Other malignancies	3543	10.9	297	12.4	3246	10.8	
Other COD	3121	9.6	270	11.3	2851	9.5	
Infectious CODs	1316	4.0	133	5.5	1183	3.9	
COPD	996	3.1	49	2.0	947	3.1	
Renal	551	1.7	88	3.7	463	1.5	
Accident or suicide	549	1.7	19	0.8	530	1.8	
Diabetes mellitus	524	1.6	68	2.8	456	1.5	
Dementia	339	1.0	21	0.9	318	1.1	
Cirrhosis	314	1.0	12	0.5	302	1.0	
Unknown	265	0.8	28	1.2	237	0.8	

COD, cause of death; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MDS, myelodysplastic syndrome.
[a]p value is from Chi-square test for categorical variables and Wilcoxon rank-sum for continuous variables.
[b]Percentages represent frequency for patients with an event.

Limitations

- Despite its size, our study has several limitations as follows:
  - It was a retrospective study
  - Clinical, molecular, cytogenetics data, and risk scores could not be analyzed nor adjusted for because they are not available in SEER
  - A large proportion of the study population had an undefined form of MDS, which limits the interpretation of the results
  - ICD-O-3 codes are inconsistent with WHO classifications

Conclusions

- We found a statistically significant association between race and OS in favor of Black patients (HR, 0.79; 95% CI, 0.76-0.83; p<0.001), with mOS of 33 months versus 26 months for Black patients compared with White patients
- This finding was unexpected and needs to be further investigated, specifically the contribution of the MDS-NOS group as codified in SEER
- Our findings raise questions regarding the adequacy of coding and classification of MDS in United States cancer registries
- We also confirm the high frequency of CVD as an attributed COD in SEER and its continued importance in the clinical management of patients with MDS

References

- American Cancer Society. Cancer Facts & Figures for African Americans 2019-2021. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-facts-and-figures-for-african-americans/cancer-facts-and-figures-for-african-americans-2019-2021.pdf
- Blackwell M, et al. *Stata J*. 2009;9(4):524-546.
- Brunner AM, et al. *Blood Adv*. 2017;1(23):2032-2040.
- Font P, et al. *Ann Hematol*. 2013;92(1):19-24.
- Goksu SY, et al. *Leuk Lymphoma*. 2022;63(7):1651-1659.
- Kirtane K, Lee SJ. *Blood*. 2017;130(15):1699-1705.
- Komrokji RS, et al. *Leuk Res*. 2010;34(1):59-62.
- Nazha A, et al. *Blood Cancer J*. 2017;7(9):e602.
- Steensma DP. *Curr Hematol Malig Rep*. 2012;7(4):310-320.
- SEER*Stat Database: Incidence - SEER Research Plus Data, 18 Registries, Nov 2020 Sub (2000-2018). Surveillance, Epidemiology, and End Results (SEER) Program. www.seer.cancer.gov.
- Zandberg DP, et al. *Leuk Lymphoma*. 2013;54(2):304-309.
- Zeidan AM, et al. *Blood Rev*. 2019;34:1-15.

Acknowledgments

- Medical writing support was provided by Meredith Rogers, MS, CMPP (The Lockwood Group, Stamford, CT, USA), and was funded by Daiichi Sankyo, Inc. Editorial support was provided in accordance with Good Publication Practice guidelines (ismpp.org/gpp-2022)

Presented at the Tenth Annual Meeting of the Society of Hematologic Oncology (SOHO 2022), September 28-October 1, 2022, Houston, TX, USA