International Journal of Cancer Medicine

Research Article | Vol 6 Issue 3

Secondary Malignancies after among Patients with Myelodysplastic Syndrome

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Received: January 27, 2022; Accepted: February 08, 2023; Published: February 15, 2023

ABSTRACT

BACKGROUND

Myelodysplastic syndromes comprise a group of clonal hematopoietic stem cell (HSC) disorders characterized by ineffective hematopoiesis and dysplastic changes in one or more myeloid lineages. Our objective was to analyze the SEER data to determine the risk of developing secondary malignancies after a primary diagnosis of MDS.

METHODS

This is a retrospective study. Frequencies of reported MDS were obtained from the SEER Program. Multiple primary-standardized incidence ratios (MP-SIR) were used to calculate standardized incidence ratios (SIRs) and absolute excess risk (AER) in patients with a primary diagnosis of MDS between 2001-2019.

RESULTS

The total number of patients with MDS reported between 2011-2019 was n = 11,431. Males formed 59.51% and females 48.41%. The number of deaths attributable to MDS decreased from 2011 to 2018, from 4.6 to 2.6 per 100,000 patients. There was an estimated 4.1 male deaths and 3.1 female deaths attributable to MDS. Applying the age, sex, and race-specific incidence rates of MDS in the SEER population for 2011-2019, the age-adjusted incidence rate for patients 85+ was the highest for white males with a rate of 103.3 (95%CI 97.9-109.0). The expected number of tumors for the general population was 868 and the observed number of secondary cancers (excluding leukemias) was n = 1,038. The ratio O/E was 1.2 suggesting that the risk for secondary malignancies in patients with MDS is greater than the general population.

CONCLUSION

The SIR was 1.2 suggesting that the risk for secondary malignancies in patients with MDS is greater than the general population and often includes cancer of the oropharynx, Kaposi's sarcoma, cancer of the esophagus and the stomach. The exact mechanism behind the development of these secondary malignancies is not well-defined. Additional studies will be needed to determine the reasons why some patients have a higher risk of developing secondary cancers after a primary diagnosis of MDS.

Citation: Jacqueline Nieto Maria, Secondary Malignancies after among Patients with Myelodysplastic Syndrome. Int J Can Med J 6(3): 142-148.

KEYWORDS

Myelodysplastic syndromes; Incidence; Secondary malignancies; Latency; SEER; Cumulative survival

INTRODUCTION

Current United States data estimates that approximately 16 million patients diagnosed with cancer are alive today [1]. Data on causes of secondary malignancies among patients with Myelodysplastic Syndrome (MDS) is limited. Our objective herein is to identify MDS survivors who may be at increased risk of developing secondary malignancies and target these patients for increased surveillance and participation in prevention programs. Myelodysplastic syndromes comprise a group of clonal hematopoietic stem cell (HSC) disorders characterized by ineffective hematopoiesis and dysplastic changes in one or more myeloid lineages. These changes often lead to cytopenias and potential progression to acute myeloid leukemia (AML) [2].

MDS typically affects men and women in their late 60's to early 70's. In fact, the annual incidence of MDS is higher for those aged >70 years old (20 cases per 100,000), when compared to the general population (1-5 cases per 100,000) [3]. Importantly, the true annual incidence of MDS in individuals aged >65-years may be even higher than reported at an estimated 75 cases per 100,000. This discrepancy is most likely due to the underreporting of MDS in several cancer registries. As an example, the Surveillance, Epidemiology, and End Results (SEER) Program estimates that in the general population, there are approximately 10,000 new MDS cases diagnosed annually. However, patients >65-years old made five times as many Medicare claims during that same period, suggesting that this diagnosis is underreported [4]. To date, MDS-related secondary malignancies have not been studied. This is the first analysis of the data published to establish a relationship between a diagnosis of MDS and the development of secondary malignancies.

We evaluated clinical data from the SEER Program of the National Cancer Institute (NCI) between 2011 and 2019. The SEER data provides information on cancer incidence, age adjusted incidence, death rate and cumulative relative survival rates from several cancer registries that covers approximately 48% of the US population.

Our objective is to analyze the SEER data to determine the risk of developing secondary malignancies after a primary diagnosis of MDS.

METHODS

This is a retrospective study. Frequencies of reported MDS were obtained from the SEER Program. Patients aged ≥50 years diagnosed with MDS between 2011 to 2019 were included in this study. The histopathological subtypes of MDS were identified by the International Classification of Diseases for Oncology version 3 or ICD-O-3.

Death attributable to MDS was analyzed for age, sex, and year between 2011 to 2019. The analysis compared MDS by subtype. Death attributable rate was calculated per 100,000 population. Age-adjusted incidence rates of MDS by subtype were calculated, including refractory anemia with excess blasts (9983-9984), refractory cytopenia with multilineage dysplasia (9985), myelodysplastic syndrome associated (9986) and myelodysplastic syndrome unclassifiable (9989).

We also calculated the observed cumulative survival rate or estimate of the probability of surviving all causes of death. Note that this contrasts with the relative cumulative survival rate which compares survivors from all causes of death in a specific population of cancer patients to the proportion of expected survivors in a similar population of cancer-free individuals [5]. Multiple primary-standardized

incidence ratios (MP-SIR) were used to calculate standardized incidence ratios (SIRs) and absolute excess risk (AER) in patients with a primary diagnosis of MDS between 2001-2019. Patients with a diagnosis of leukemia were excluded. The SIR, or relative risk, was measured by dividing the observed number of secondary malignancies by the expected number of total cancers in the general population. For further analysis, the SIRs for specific subgroups were stratified by gender, race, calendar year and latency period following the initial diagnosis of MDS. The AER is a measure of the clinical burden of cancer and was defined as excess cancer per 10,000 persons annually [6]. All statistical tests of significance were two-sided, and a P value <0.05 was considered statistically significant. We excluded patients with AML and determined the rates of occurrence of solid tumors among patients with MDS.

RESULTS

Characteristics of patients with MDS aged 50 and older between 2011-2019 are presented in Table 1 as per the SEER database. The total number of patients with MDS reported between 2011-2019 was n = 11,431. Males formed 59.51% and females 48.41%. The subtypes represented by ICD-O-3 include refractory anemia with ring sideroblasts which was seen in 7.2%, refractory anemia with excess blasts which was seen in 17.31%, refractory cytopenia with multilineage dysplasia which was seen in 9.19%, myelodysplastic syndrome associated which was seen in 4.43% of patients, and myelodysplastic syndrome unclassifiable which was seen in 61.81% of patients. Frequencies of race were reported as white 83.22%, black 5.7%, Asian 10.62% and other 0.42%. The analysis included patients aged 50-years to 85+-years old. A higher percentage of patients with MDS, 25.90%, was reported in those 85+.

The number of deaths attributable to MDS decreased from 2011 to 2018, from 4.6 to 2.6 per 100,000 patients. There was an estimated 4.1 male deaths and 3.1 female deaths attributable to MDS. In Figure 1A and Figure 1B, death attributable to MDS was found to be highest for patients 85-years and older at 10.4 /100,000.

Characteristics	Number of Patients	Percent
Gender	11,431	
Male	6,803	59.51%
Female	4,628	40.48%
Subtype		
9982	854	7.20%
9983	2044	17.31%
9985	1085	9.19%
9986	524	4.43%
9989	7296	61.81%
Race	11431	
White	9514	83.22%
Black	654	5.70%
Asian	1215	10.62%
Other	48	0.42%
Age	11431	
50-54	239	2.09%
55-59	454	3.97%
60-64	731	6.39%
65-69	1235	10.80%
70-74	1672	14.62%
75-79	2012	17.60%
80-84	2127	18.60%
85+	2961	25.90%

Table 1: Characteristics of patients with myelodysplastic syndrome Aged 50 and older.

In Table 2, men had a higher incidence rate of MDS compared to women. When adjusted for age, the incidence of MDS in men was approximately 21.2 cases per 100,000 (95% CI 20.7 to 21.7/100,000) compared to 10.5 cases per 100,000 for women (95% CI, 10.1-10.8/100,000). When stratified by race, whites were noted to have the highest incidence rate. American Indians/Alaska Natives and Asian/Pacific Islander women had lower rates (Figure 2).

Applying the age, sex, and race-specific incidence rates of MDS in the SEER population for 2011-2019, the age-adjusted incidence rate for patients 85+ was the highest for white males with a rate of 103.3 (95%CI 97.9-109.0). The lowest rate was for women of another race at 36.4 (95%CI 30.7-42.8). Age-adjusted incidence rates of MDS by subtype were calculated. They were higher for patients with refractory anemia with excess blasts (Figure 3). The

age-adjusted incidence rate of MDS unclassifiable was 3.3
in 2010 and decreased to 2.0 in 2019 (Table 3).

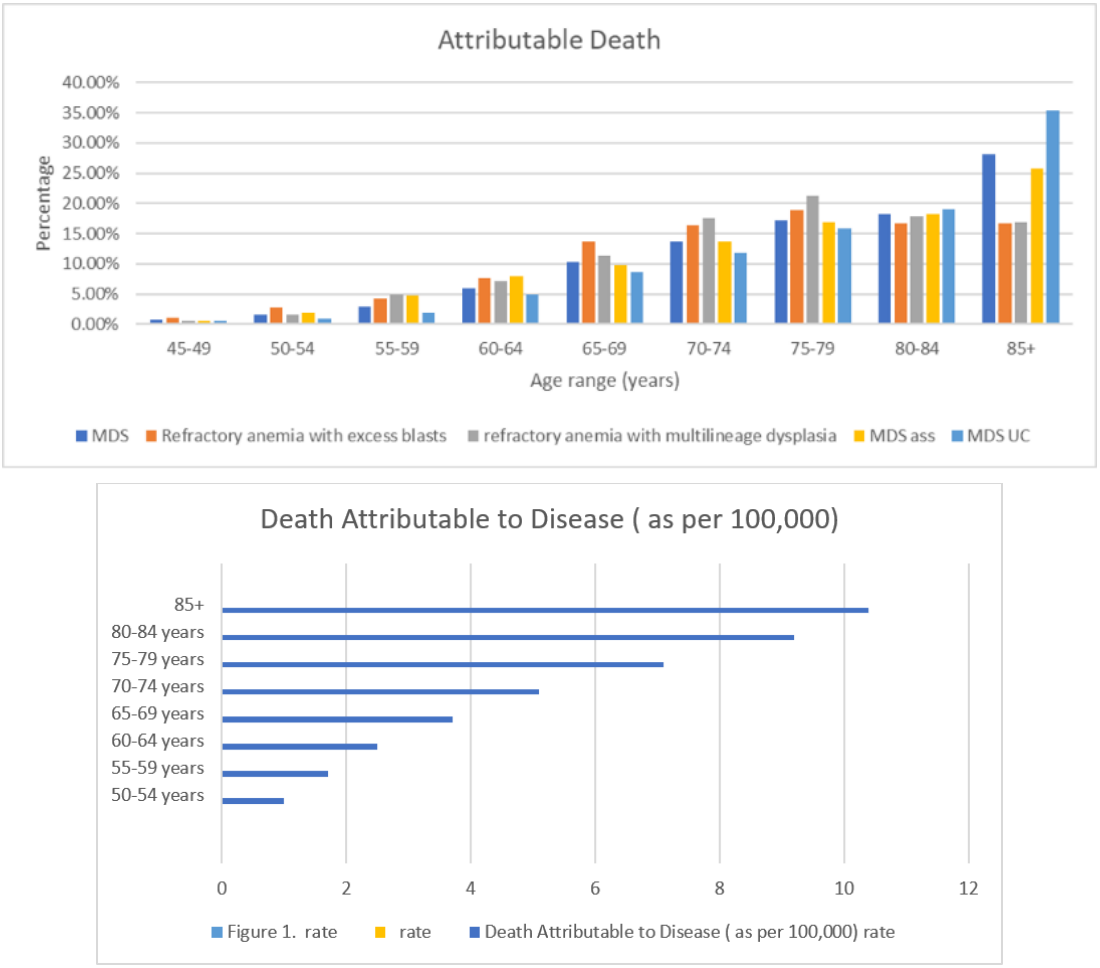

Figure 1: Death attributable to myelodysplastic syndrome.

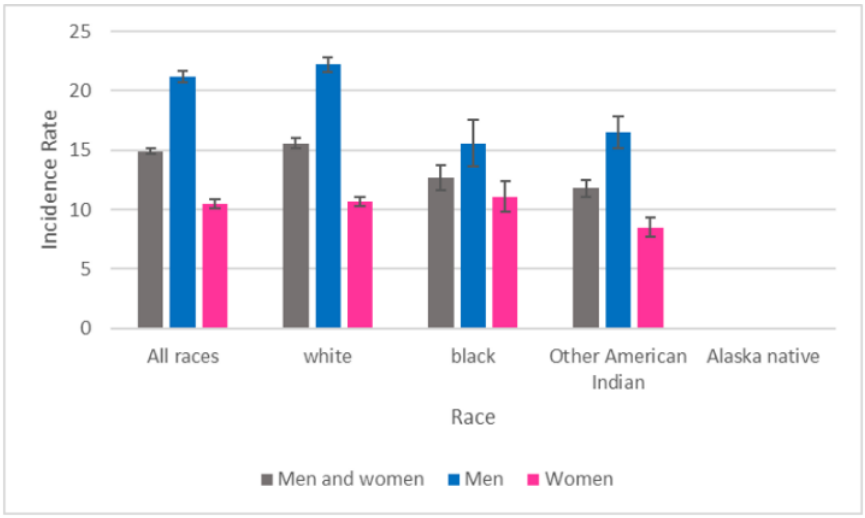

Figure 2: Age-adjusted incidence rates of myelodysplastic syndromes by sex and race in the United States, 2011-2019: The surveillance, epidemiology, and end results program.

Variable	Rate (95% CI confidence Interval)		
	Men and Women	Men	Women
All races	14.9(14.7-15.2)	21.2(20.7-21.7)	10.5(10.1-10.8)
White	15.6(15.2-15.9)	22.2(21.6-22.8)	10.7(10.3-11.0)
Black	12.7(11.7-13.8)	15.6(13.7-17.6)	11.1(9.8-12.4)
Other American Indian	11.8(11.1-12.5)	16.5(15.3-17.9)	8.5(7.7-9.3)
Alaskan native			

Table 2:

	RARS	RAEB	RAMD	MDS-A	MDS-U	All MDS
2010	0.4	0.8	0.5	0.2	3.3	5.1
2011	0.4	0.7	0.6	0.2	3.1	5
2012	0.3	0.8	0.5	0.2	3.1	4.9
2013	0.3	0.8	0.4	0.2	2.7	4.5
2014	0.3	0.7	0.4	0.2	2.5	3.9
2015	0.3	0.7	0.4	0.2	2.4	4
2016	0.3	0.7	0.4	0.2	2.5	4
2017	0.3	0.5	0.3	0.2	2.5	3.8
2018	0.3	0.7	0.3	0.2	2.1	3.6
2019	0.2	0.7	0.4	0.2	2	3.5

Table 3: Age adjusted rates MDS by subtype.
RARS: Refractory Anemia with Ring Sideroblasts; RAMD: Refractory Anemia with Multilineage Dysplasia; RAEB: Refractory Anemia with Excess Blasts; MDS-A: MDS Associated; MDS-U: MDS Unclassifiable.

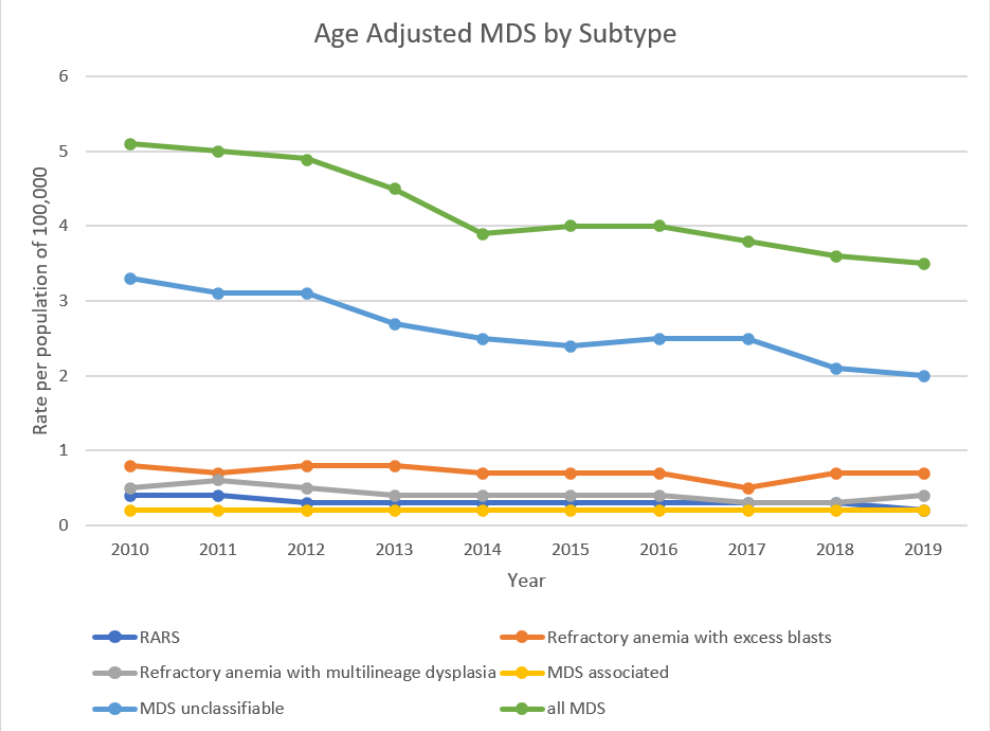

Figure 3: Age adjusted MDS by subtype.

Included in our MDS survival analysis were 7328 patients with no specified subtype. Their cumulative observed survival at 60 months was 25.9%; the relative cumulative survival was 33.7% (95% CI of 32.2%-35.3%). The lowest survival rate was observed among patients with refractory anemia with excess blasts (n = 1,429). The cumulative observe survival was 13.6% at 60 months. The relative cumulative survival at 60 months was 15.6% (95% CI, 13.2%-18.2%).

Secondary Malignancies after Diagnosis of MDS between 2001-2019

A total of 14,231 patients were followed starting two months after their diagnosis of MDS. Two months was used as the default period. The total observation period was 48,082.57 person-years with a mean of 3.38 person-years at risk. The average age at diagnosis was 74.27.

The expected number of tumors for the general population was 868 and the observed number of secondary cancers (excluding leukemias) was n = 1,038. The ratio O/E was 1.2 suggesting that the risk for secondary malignancies in patients with MDS is greater than the general population.

The SIR of all sites except leukemias was 1.2. The AER of all sites except leukemias was 35.29 excess risk per 10,000 persons per year.

Subsequent analysis of cancers of the oral cavity showed that the SIR was 5.43 (95% CI 1.48- 13.91), and for Kaposi's sarcoma was 6.20 (95% CI 1.28-18.11). Both were significant. The esophagus showed SIR of 1.85 (95% CI 1.14-2.82) while stomach had an SIR of 1.56 (95% CI 1.03-2.28).

The following analysis had a latency at 1-year, 5-years and 10-years, which calculates the excess risk in the first year after diagnosis of MDS versus 5-years and 10-years. The risk for developing secondary cancers in the first few months (2 months -11 months) was higher 1.33 compared to the general population.

DISCUSSION

This analysis used a large population-based data set to evaluate the incidence and survival of MDS in the United States. The SEER Program provides data on cancer diagnoses, treatment, and survival from 18 Cancer Registries across the United States.

Our data showed an increase in incidence rate in 2010 and 2011 at 5.1. Since 2012, that rate has been slowly decreasing, most recently 4.1 as of 2019, likely due to underreporting and underdiagnosis. As an example, in the NAACCR/SEER study, physician offices only reported approximately 4% of their MDS cases to these registries [6]. Notably, the incidence rate among elderly patients remains elevated at 10.5 cases in those aged 65years - 69 years old and up to 61 cases in those aged ≥85 years.

Subgroup analysis identified a gender disparity among the age-adjusted incidence rates of patients with MDS. It was highest in white males aged 85 and older with a rate of 103.3 (95%CI 97.9-109.0) and the lowest in women of another race with a rate of 36.4 (95%CI 30.7-42.8). Survival data revealed that male patients had shorter survival than female patients in the same age subgroups. Subgroup analysis by race and gender revealed that males had a higher probability of mortality when compared to females in the same race/ethnicity groups. Notably, males were noted to have more comorbidities at diagnosis (cardiovascular disease, severe pulmonary disease, severe liver disease) which may explain their increased mortality. In fact, cohort-based studies have shown that patients with MDS and these underlying comorbidities have a greater risk of death [4,7-10]. Furthermore, the presence of these comorbidities may influence treatment strategies and/or aggressiveness of treatment leading to increased mortality. Previous studies have reported similar results in terms of incidence rates, gender disparity and survival distributions based on race-ethnicity [11-13].

MIP-SIR was used to evaluate secondary malignancies in patients with a primary diagnosis of MDS between 2001-2019. The expected number of tumors for the general population was 868 and the observed number of secondary cancers (Excluding leukemias) was 1,038. The SIR was 1.2 suggesting that the risk for secondary malignancies in patients with MDS is greater than the general population

and often includes cancer of the oropharynx, Kaposi's sarcoma, cancer of the esophagus and the stomach. The exact mechanism behind the development of these secondary malignancies is not well-defined. It may be multifactorial due in part to genetic predisposition, certain environmental or other risk exposures and delayed effects from previous chemotherapy. Previous studies have shown an association between smoking and alcohol intake and the development of MDS [14]. The same risk factors have been proven to increase the risk of oropharyngeal cancer.

Additional studies will be needed to determine the reasons why some patients have a higher risk of developing secondary cancers after a primary diagnosis of MDS. Genetic studies may further reveal a relationship between MDS and development of secondary cancers that may warrant primary and secondary prevention strategies.

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