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Research Article

Factors predicting progression to AML and use of allogeneic hematopoietic stem cell transplant in patients with MDS

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Abstract

Background: Risk-benefit assessment data for myelodysplastic syndrome (MDS) treatment are scarce. We characterized baseline factors and clinical course data in patients with MDS who progressed to acute myeloid leukemia (AML) or underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) in a real-world observational study using demographic, disease, and treatment claims data from a large US administrative healthcare database.

Methods: The study period was from July 1, 2002, to June 30, 2018. The incidence rates (per 1000 patients/year) of progression to AML and undergoing allo-HSCT were evaluated.

Results: The study population comprised 15,680 patients identified using International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification codes for MDS. Mean (range) follow-up duration was 2.8 (0–11.8) and 2.7 (0–11.8) years for the AML and allo-HSCT cohorts, respectively. Risk of progression to AML was high in all age groups, with highest incidence rates in patients aged < 18 years and 50–69 years. Use of azacitidine, indicating higher-risk disease, was associated with both progression to AML and undergoing allo-HSCT. The rate of allo-HSCT was low.

Conclusion: These data emphasize the importance of assessing eligibility to allo-HSCT in a consistent manner.

Keyword: Myelodysplastic syndrome; acute myeloid leukemia; allogeneic hematopoietic stem cell transplantation

Abbreviations: AIDS: Acquired Immune Deficiency Syndrome; Allo-HSCT: allogeneic hematopoietic stem cell; transplantation; AML: acute myeloid leukemia; C: case; CCI: Charlson Comorbidity Index; CI: confidence interval; HCT-CI: Hematopoietic Cell Transplantation-specific Comorbidity Index; HLA: human leukocyte antigen; HR: hazard ratio; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification; IPSS: International Prognostic Scoring System; IPSS-R: International Prognostic Scoring System revised version; IR: incidence rate; MDS: myelodysplastic syndrome; NRM: non-relapse mortality; Optum: Optum® Clinformatics™ Data Mart; SD: standard deviation; SEER; Surveillance, Epidemiology, and End Results

Background

Myelodysplastic syndrome (MDS) represents a heterogeneous group of clonal hematopoietic malignancies associated with progressive bone marrow failure, inadequate hematopoiesis, and cytogenic abnormalities [1-3]. MDS is more common in older patients, with median patient age at diagnosis of 70–75 years [4,5]; the incidence of idiopathic MDS is 4.5/100,000 persons per year in the general population and rises to 26.9–55.4/100,000 persons per year in those aged ≥ 70 years [6]. At the early stage of disease, MDS is mostly asymptomatic and undiagnosed [1]. Over time, patients may experience shortness of breath and fatigue, and develop anemia (refractory to folate and vitamin B12 treatment), neutropenia, and infections as well as thrombocytopenia [1,2]. To assist with treatment decisions, the International Prognostic Scoring System (IPSS) and its revised version (IPSS-R) were developed to assess

prognosis in untreated adult patients with idiopathic MDS [7,8]. Depending on the IPSS risk score, median survival times for patients with MDS not treated with chemotherapy are 0.8 (very high risk), 3.0 (intermediate risk), and 8.8 years (very low risk) [7]. Some patients with MDS may experience prolonged survival with a more chronic disease course; however, other patients with a more severe form of MDS may progress to acute myeloid leukemia (AML) [7]. The estimated risk of progression to AML is approximately 3% in the very low risk group and up to 84% in the very high-risk group (risk groups defined per the World Health Organisation PSS) [9]. Historically, the MDS survival data were not collected by the Surveillance, Epidemiology, and End Results (SEER) Program. Reporting of these data by SEER was initiated in 2001.

There is a significant unmet need for safe and effective MDS treatments. Currently, MDS therapy adopts a risk-dependent approach. In patients with higher-risk MDS and clinically relevant cytopenias, the National Comprehensive Cancer Network guidelines recommend hypomethylating agents such as azacitidine and decitabine as first-line treatment; lenalidomide is recommended for use in the subgroup of patients with a 5q chromosome deletion [8]. Long-term myelosuppressive therapy with hypomethylating agents and lenalidomide can present challenges in older patients [10]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only potentially curative option for MDS. Because of significant morbidity and mortality that may be associated with allo- HSCT, in particular graft-versus-host disease, allo-HSCT tends to be reserved for patients who have good performance status and few co-morbidities [10,11]. The decision to proceed with allo-HSCT is based on disease characteristics, including cytogenetics, patient age, performance status, co-morbid conditions, and psychosocial status, as well as patient preference and availability of a caregiver [12]. Currently, allo-HSCT is primarily offered to patients with higher-risk MDS and to those who progress to AML. However, patients with MDS who progress to AML tend to have a more aggressive disease course, often resulting in a worse performance status and generally poorer health than patients who do not progress; therefore, those who progress to AML are more likely to become unsuitable candidates for allo-HSCT. Allo-HSCT procedure earlier in the disease course has the potential to improve outcomes [12], although the risk of complications such as transplant relapse and graft-versus-host disease must be considered [13]. Prospective trials comparing transplant and non-transplant strategies have recently been completed, but results have not yet been published. Using the medical and pharmacy claims records from a large US administrative healthcare claims database, this study characterized the clinical course of patients with MDS who progressed to AML or underwent allo-HSCT and investigated baseline factors associated with progression to AML or receiving allo-HSCT.

Methods

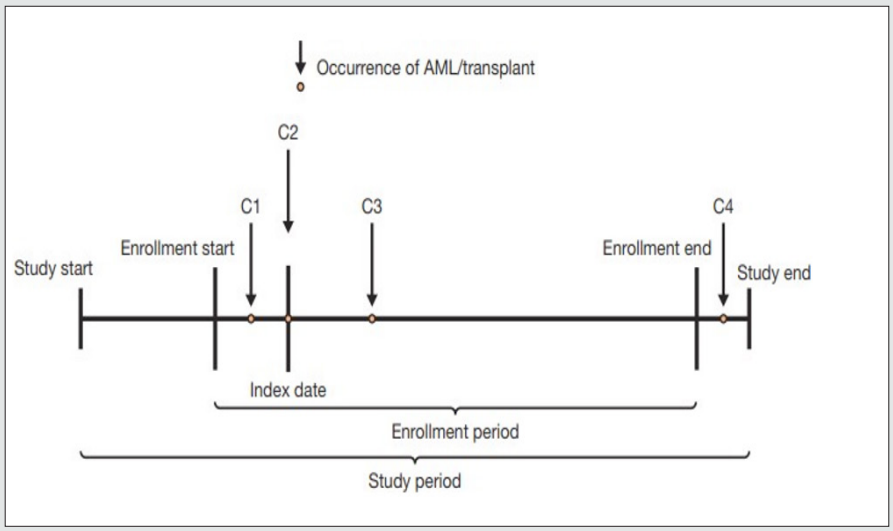


Figure 1: Study design.

C1: patient will be removed from the cohort considered for IR calculation.

C2: patient will be removed from the cohort considered for IR calculation.

C3: the event will be considered as an incident event (the follow-up end will be censored at this event date, and the person-years will be calculated as C3 date – index date).

C4: the event will not be considered as an incident event. All cases are independent of any other case.

AML acute myeloid leukemia, C case, IR incidence rate.

Study design, data sources, and patient population: Data from a large US administrative healthcare database (Optum® Clinformatics™ Data Mart [Optum]) were used for this retrospective, real-world observational study. The Optum database contains claims information and enrollment data on approximately 35 million patients from 2002 onwards. Available data include demographic variables, diagnostic codes, and treatment information. Study design is provided in Figure 1. Patients of any age with a diagnosis of MDS based on the International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification (ICD-9-CM or ICD-10-CM) codes 238.72, 238.73, 238.74, and 238.75 were identified. Patients with at least two claims' records with a relevant diagnostic code between 14 and 365 days apart were eligible. The index date was defined as the date of the first observed claim record between July 1, 2002, and December 31, 2014; the study period was from July 1, 2002, to June 30, 2018.

Study variables: Patients who received blood transfusions were identified based on the ICD-9-CM or ICD-10-CM procedure codes in the 6-month baseline period before the index date. Patients with concomitant medication use at the 6-month baseline period were identified based on pharmacy claims records. The co-morbidities of interest were identified among the 50 most frequent co-morbid conditions recorded in the study cohort during the 6-month baseline period for each patient (Table 1). For a co-morbidity to be verified, a confirmation of diagnosis of that co-morbidity was required by at least two records separated by > 14 days. The Charlson Comorbidity Index (CCI) score was calculated to describe the overall burden of disease using a published algorithm on 11 co-morbidities in the 6-month baseline period prior to the index date for every eligible patient (Table 2) [14]. The co-morbidities included in the CCI score calculation were dementia, chronic obstructive pulmonary disease, rheumatic diseases, liver disease (mild and moderate-to-severe), complicated diabetes mellitus (type 1 or type 2), hemiplegia, kidney disease, malignancy, metastatic solid tumor, and acquired immunodeficiency syndrome. The Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) scale could not be calculated in this study due to laboratory data being unavailable.

Table 1: Baseline characteristics of the overall MDS study population.

Characteristic	N = 15,680
Sex	8395 (53.5)
Female	7285 (46.5)
Age at index date, mean (SD)/median, years	73.4 (12.19)/77.0
Prior blood transfusion	232 (1.5)
Number of blood transfusions	
< 5	202 (1.3)
5-20	29 (0.2)
≥ 21	1 (< 0.1)
Concomitant medication	
Corticosteroids	4515 (28.8)
Acetaminophen	4018 (25.6)
Furosemide	3142 (20.0)
Hydrocodone	2859 (18.2)
Metoprolol	2499 (15.9)
Levothyroxine	2628 (16.8)
Azacitidine	565 (3.6)
Co-morbidities[a]	
Anemia	8366 (53.4)
Essential hypertension	5946 (37.9)
Diseases of blood and blood-forming organs (diseases mentioned in the present list only)	4112 (26.2)
Hyperlipidemia	3563 (22.7)
Diabetes mellitus (type 1 or type 2)	3437 (21.9)
Arteriosclerosis (coronary artery)	2165 (13.8)
Arrhythmia	1943 (12.4)
Renal failure (chronic)	1830 (11.7)
Thrombocytopenia	1774 (11.3)
Iron-deficiency anemia	1556 (9.9)
Fatigue	1520 (9.7)

Malaise	1479 (9.4)
Bone marrow failure	1415 (9.0)
Dyspnea/shortness of breath	1381 (8.8)
Hypothyroidism	1294 (8.3)
Pancytopenia	1098 (7.0)
Osteoarthritis	1002 (6.4)
Arthralgia	864 (5.5)
Lung disorder	860 (5.5)
Neutropenia	778 (5.0)
Chest pain	772 (4.9)
Gastroesophageal reflux disease	747 (4.8)
Blood disorder	668 (4.3)
Abdominal pain	667 (4.3)
Edema	562 (3.6)
CCI score[b] (14)	
Malignancy	3446 (22.0)
Kidney disease	2533 (16.2)
Chronic obstructive pulmonary disease	2289 (14.6)
Diabetes mellitus (complicated; type 1 or type 2)	1009 (6.4)
Rheumatic diseases	626 (4.0)
Liver disease (mild)	495 (3.2)
Solid tumor (metastatic)	282 (1.8)
Dementia	240 (1.5)
Liver disease (moderate-to-severe)	128 (0.8)
Hemiplegia	71 (0.5)
AIDS	16 (0.1)

Data are n (%) unless indicated otherwise. Only characteristics for ≥ 3% have been included (except for the CCI). AIDS acquired immune deficiency syndrome, CCI Charlson Comorbidity Index, MDS myelodysplastic syndrome, SD standard deviation.

[a]Co-morbidity of a patient was recorded if there were ≥ 2 diagnoses separated by > 14 days.

[b]CCI score was calculated using at least two diagnoses (on two different dates) of each of the 11 conditions.

Table 2: Incidence rates for progression from MDS to AML.

Baseline characteristic	Number of patients	Number of events	Incidence proportion, %	Total person- years	Incidence rate (per 1000 patients per year)
Total number of patients with MDS with no baseline incidence	14,829	763	5.2	40,907.34	18.65
Sex					
Male	7888	473	6	20,153.51	23.47
Female	6941	290	4.2	20,753.83	13.97
Age group, years					
< 18	41	4	9.8	125.23	31.94
18–39	196	15	7.7	519.66	28.86
40–49	401	30	7.5	1237.86	24.24
50–59	1107	99	8.9	3146.21	31.47
60–69	2375	194	8.2	6398.75	30.32
70–79	4805	259	5.4	14,450.00	17.92
80–89	5904	162	2.7	15,029.63	10.78
Concomitant medications					
Decitabine	115	24	20.9	159.89	150.1

Azacitidine	418	82	19.6	623.15	131.59
Hydrocodone	2677	137	5.1	6812.56	20.11
Acetaminophen	3762	183	4.9	9686.99	18.89
Rituximab	144	7	4.9	293.34	23.86
Azathioprine	83	4	4.8	228.05	17.54
Corticosteroids	4207	196	4.7	10,865.73	18.04
Levothyroxine	2512	102	4.1	6983.85	14.61
Metoprolol	2359	84	3.6	6151.73	13.65
Danazol	32	1	3.1	61.56	16.24
Furosemide	3005	90	3	6874.55	13.09
Co-morbidities					
Pyrexia	109	14	12.8	192.85	72.6
Epistaxis	63	8	12.7	114.27	70.01
Increased body temperature	18	2	11.1	24.08	83.07
Neutropenia	594	62	10.4	1356.95	45.69
Leukopenia	371	38	10.2	1020.2	37.25
Pancytopenia	901	82	9.1	1853.3	44.25
Lymphoma	333	30	9	682.63	43.95
Lymphoma or Hodgkin's	354	31	8.8	728.76	42.54
disease[a]					
Blood disorder	611	49	8	1583.54	30.94
Bone marrow failure	1169	93	8	2482.72	37.46
Diseases of blood and blood- forming organs (below- mentioned diseases only)	3657	275	7.5	8661.46	31.75
Bruising	68	5	7.4	145.5	34.36
Hodgkin's disease	27	2	7.4	53.27	37.54
Leukocytosis	255	18	7.1	493.01	36.51
Thrombocytopenia	1554	108	7	3512.43	30.75
Vomiting	236	15	6.4	449.05	33.4
Aplastic anemia	290	18	6.2	692.08	26.01
Abdominal pain	619	38	6.1	1469.85	25.85
Pain	115	7	6.1	229.91	30.45
Chest pain	708	40	5.7	1503.5	26.6
Headache	125	7	5.6	335.72	20.85
Pneumonia	351	19	5.4	696.32	27.29
Dizziness	245	13	5.3	625.24	20.79
Hyperlipidemia	3373	167	5	9144.67	18.26
Lung disorder	760	37	4.9	1379.71	26.82
Cellulitis	285	13	4.6	634.2	20.5
Dyspnea/shortness of breath	1273	58	4.6	2522.3	22.99
Anemia	7909	355	4.5	20,689.83	17.16
Gastroesophageal reflux	695	31	4.5	1707.45	18.16
disease					
Dehydration	158	7	4.4	243.94	28.7
Arteriosclerosis of a coronary	2067	88	4.3	4922.33	17.88
artery					
Malaise	1363	58	4.3	2967.13	19.55

Hypothyroidism	1218	51	4.2	3244.01	15.72
Essential hypertension	5647	230	4.1	14,766.35	15.58
Fatigue	1403	58	4.1	3063.8	18.93
Osteoarthritis	966	39	4	2627.01	14.85
Diabetes mellitus (type 1 or type 2)	3294	119	3.6	8633.08	13.78
Arthralgia	820	29	3.5	2287.51	12.68
Arrhythmia	1875	62	3.3	4180.69	14.83
Autoimmune hemolytic anemia	33	1	3	69.32	14.43
Edema	539	12	2.2	1188.8	10.09
Iron-deficiency anemia	1522	34	2.2	3951.02	8.61
Acute renal failure	386	8	2.1	738.99	10.83
Back pain	193	4	2.1	444.58	9
Chronic renal failure	1782	35	2	4184.76	8.36
Appendicitis	2	–	0	9.3	–
Abnormal chest X-ray	80	-	0	119.37	–
Hyperthermia	1	-	0	0.83	–
Petechiae	6	-	0	8.76	–

AML diagnosed with 205.0x (ICD-9-CM), C92.Ax, and C92.6x (ICD-10-CM). Patients with > 1 claim for AML made ≥ 14 days apart were included in the analysis; patients with AML in the 6-month baseline (including index MDS date) were removed from the analysis. The incidence event date was the date of the first claim for AML.

AML acute myeloid leukemia, ICD-9-CM International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-10-CM International Classification of Diseases, Tenth Revision, Clinical Modification, MDS myelodysplastic syndrome.

[a]Total count of lymphoma or Hodgkin's disease does not equal the sum of separate lymphoma and Hodgkin's disease entries due to an overlap in patient population for both conditions.

Study outcomes and statistical analyses: Patients with at least two claims that included a relevant ICD-9-CM or ICD-10-CM code for AML (ICD-9-CM: 205.0x; ICD-10-CM: C92.Ax, and C92.6x) or allo-HSCT (ICD-9-CM: V42.4, V42.81, V42.9, 279.50, 996.85; ICD-10-CM: T86.03, Z94.81, Z94.9x, Z94.6x) ≥ 14 days from the index date + 1 day and the study end date were included in the analysis. Baseline characteristics were analyzed descriptively. Only patients without an AML diagnosis or allo-HSCT procedure in the baseline period or at index date were included in the calculation of the incidence rates (IRs) for progression from MDS to AML or undergoing allo-HSCT. IRs were evaluated for the overall cohort and per baseline characteristics (age [groups of < 18, 18–39, 40–49, 50–59, 60–69, 70–79, 80–89 years], sex, concomitant medication, prior procedures, and co-morbidities), and were reported per 1000 patients per year.

To evaluate factors associated with progression to AML and undergoing allo-HSCT, logistic regression modelling was used to identify baseline variables for inclusion in subsequent Cox multivariate models, which were used for covariate selection (at a significance level of 0.05). The list of covariates included age (categories of < 50, 50–69, and 70–89 years), sex, baseline blood transfusions, concomitant medications, and co-morbidities (50 most frequently reported conditions, vide supra). The co-morbidities were included in the model as a categorical variable (presence or absence at baseline) and were excluded using a stepwise method based on the significance assessment. A multivariate Cox regression model was then constructed to determine baseline characteristics associated with occurrence of AML or undergoing allo-HSCT, expressed as adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). The basic assumptions of the models, such as linear relationship between the predictor and the hazard, were observed in the model along with the assumptions of constant hazard rate with time. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient population: 19 of 37,313 patients initially identified under ICD-9-CM and ICD-10-CM codes for MDS, 15,680 were eligible for inclusion and comprised the study population (Figure 2). Mean (range) follow-up duration was 2.8 (0–11.8) and 2.7 (0–11.8) years for the AML and allo-HSCT cohorts, respectively. The minimum of 0-years follow-up duration was attributed to one patient having the first diagnosis of MDS outside of the 6-month baseline period and the second immediately before being diagnosed with AML. At baseline (index date), numbers of male and female patients were comparable. The median patient age was 77.0 years (Table 1). The most common concomitant medications were corticosteroids (28.8%) and acetaminophen (paracetamol; 25.6%). Mean (± standard deviation) CCI score at baseline was 2.99 (± 1.51). The most common co-morbidities were anemia (53.4%; included as a co-morbid condition in this analysis), essential hypertension (37.9%), hyperlipidemia (22.7%), other malignancy (22.0%), and diabetes mellitus (type 1 or type 2, 21.9%).

Incidence and factors associated with progression from MDS to AML: During the study period, 5.2% of patients progressed to AML, representing an IR for progression of 18.7 per 1000 patients per year (Table 2). Progression rates were nearly twice as high in male patients (23.47 per 1000 patients per year) compared with female patients (13.97 per 1000 patients per year). Among age subgroups, the highest progression rates were seen in patients under 18 (31.94 per 1000 patients per year) and between 50 and 59 years of age (31.47 per 1000 patients per year). Patients previously treated with hypomethylating agents at baseline were likely to have the highest incidence of AML, indicating higher-risk disease. Patients younger than 50 years and those aged 50 to 69 years were more likely than patients aged 70–89 to progress to AML (Figure 3a). Receipt of azacitidine, suggesting the presence of higher-risk disease, had the strongest association with progression to AML (HR = 4.55; 95% CI: 3.59–5.76) (Figure 3a). Among co-morbidities, epistaxis had the highest association with progression to AML (HR = 3.39; 95% CI: 1.69–6.82); other co-morbidities included pyrexia, lymphoma, pancytopenia, leukopenia, and blood disorders (Figure 3a).

Incidence and factors associated with progression from MDS to undergoing allo-HSCT: During the study period, 2.8% of patients with MDS underwent allo-HSCT, representing a rate of 10.2 per 1000 patients per year (Table 3). Patients aged < 50 years at baseline were more likely to undergo allo-HSCT (HR = 47.59; 95% CI: 31.53–71.84; Figure 3b) compared with older patients. Receipt of azacitidine and decitabine, suggesting the presence of higher-risk disease, were both associated with subsequent allo-HSCT (Figure 3b). Patients who underwent allo-HSCT versus those who did not were more likely to have lymphoma (HR = 2.89; 95% CI: 2.02–4.14), pancytopenia (HR = 2.60; 95% CI: 1.99–3.40), pyrexia (HR = 2.81; 95% CI: 1.83–4.30), leukopenia (HR = 2.28; 95% CI: 1.57–3.32), blood disorder (HR =1.86; 95% CI: 1.37–2.53), or hypothyroidism (HR = 1.85; 95% CI: 1.27–2.68) as a co-morbidity reported at baseline (Figure 3b).

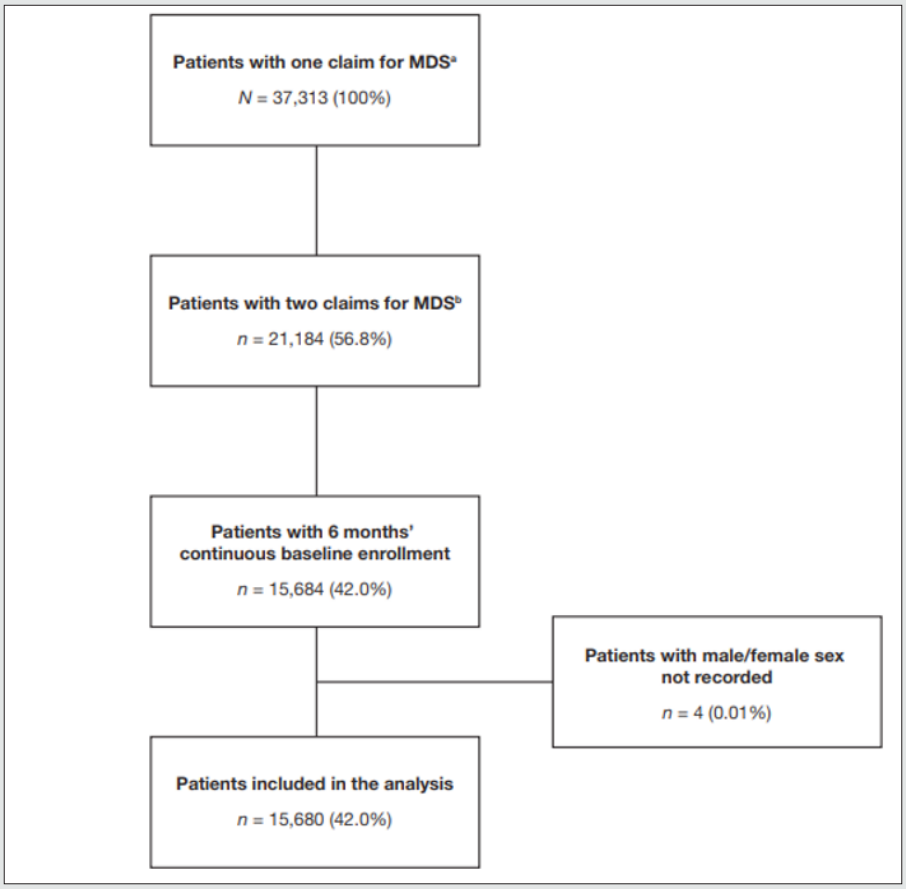
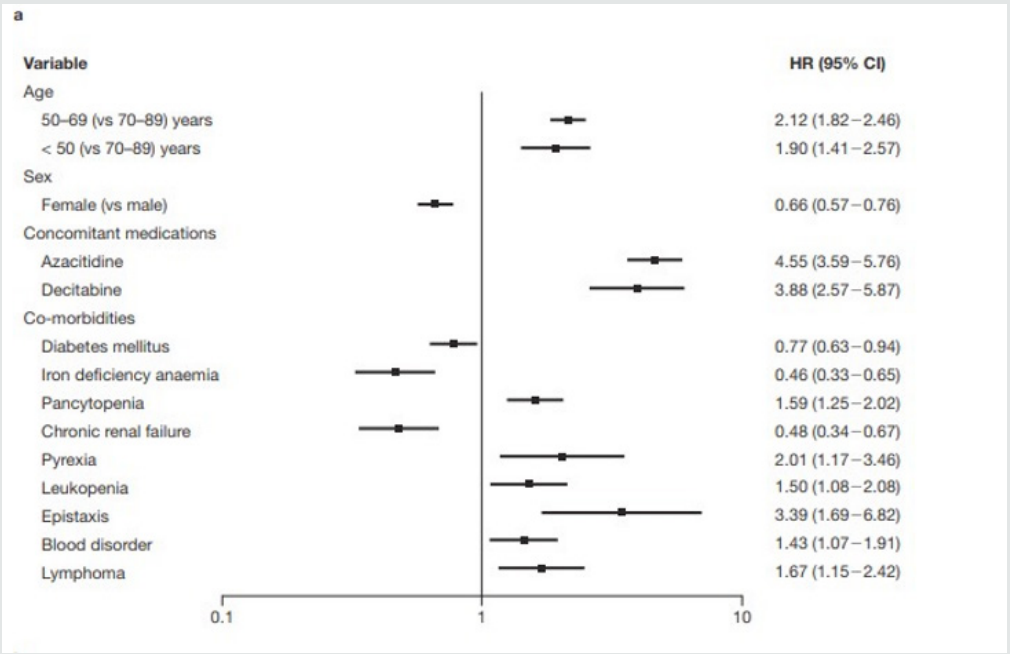


Figure 2: Patient attrition flow.

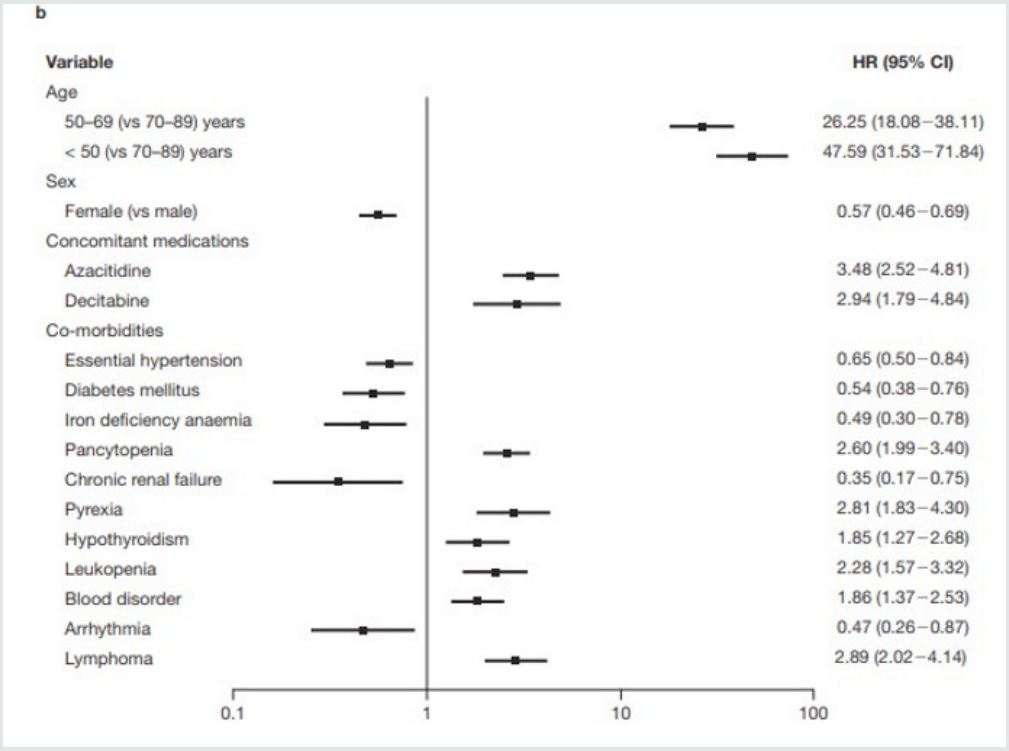
MDS was identified with ICD-9-CM or ICD-10-CM codes 238.72, 238.73, 238.74, and 238.75. Index date was the first diagnosis of MDS.

[a]> 1 MDS claims at index date were recorded for some patients.

[b]The second claim was observed 14–365 days from the first one. ICD-9-CM International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-10 CM International Classification of Diseases, Tenth Revision, Clinical Modification, MDS myelodysplastic syndrome.



a) Progression to AML (n = 14,829).



b) Advancement to all-HSCT (n = 15,484).

Figure 3: Predictive value of selected baseline variables for MDS progression to AML and advancement to allo-HSCT. Allo-HSCT allogeneic hematopoietic stem cell transplantation, AML acute myeloid leukemia, CI confidence interval, HR hazard ratio, MDS myelodysplastic syndrome.

Table 3: Incidence rates for allo-HSCT among patients with MDS.

Baseline characteristic	Number of patients	Number of procedures	Incidence proportion, %	Total patient-years	Incidence rate (per 1000 patients per year)
Total number of patients with MDS with no baseline allo-HSCT	15,484	428	2.8	41,860.12	10.22
Sex					
Male	8276	260	3.1	20,639.79	12.6
Female	7208	168	2.3	21,220.33	7.92
Age group, years					
< 18	45	18	40	98.61	182.53
18–39	209	35	16.8	523.95	66.8
40–49	409	47	11.5	1223.67	38.41
50–59	1183	149	12.6	3141.77	47.43
60–69	2538	148	5.8	6606	22.4
70–79	5042	31	0.6	14,933.80	2.08
80–89	6058	–	0	15,332.34	–
Previous medication					
Azathioprine	85	5	5.9	229.37	21.8
Acetaminophen	3963	131	3.3	9961.1	13.15
Furosemide	3107	20	0.6	7001.19	2.86
Hydrocodone	2818	97	3.4	6975.77	13.91
Metoprolol	2464	28	1.1	6315.04	4.43
Levothyroxine	2605	47	1.8	7110.38	6.61
Rituximab	148	7	4.7	294.92	23.74
Danazol	35	–	0	69.15	–
Decitabine	193	17	8.8	227.42	74.75
Azacitidine	551	44	8	753.22	58.42
Corticosteroids	4392	151	3.4	10,989.41	13.74
Co-morbidities					
Essential hypertension	5897	81	1.4	15,147.35	5.35
Malaise	1456	38	2.6	3071.74	12.37
Chest pain	758	23	3	1552.54	14.81
Hyperlipidemia	3537	75	2.1	9402.19	7.98
Iron-deficiency anemia	1552	18	1.2	4013.92	4.48
Abdominal pain	650	20	3.1	1524.43	13.12
Arteriosclerosis of a coronary	2156	22	1	5047.54	4.36
artery					
Arthralgia	853	14	1.6	2334.08	6
Appendicitis	3	1	33.3	10.36	96.54
Gastroesophageal reflux	736	21	2.9	1731.14	12.13
disease					
Osteoarthritis	998	10	1	2683.09	3.73
Back pain	206	6	2.9	453.48	13.23
Pneumonia	392	18	4.6	732.45	24.57
Chronic renal failure	1815	7	0.4	4223.32	1.66

Hypothyroidism	1280	32	2.5	3309.66	9.67
Hyperthermia	1	–	0	0.83	–
Pyrexia	162	26	16.1	218.93	118.76
Increased body temperature	42	9	21.4	32.64	275.77
Edema	554	10	1.8	1197.69	8.35
Abnormal chest X-ray	91	4	4.4	125.98	31.75
Acute renal failure	406	3	0.7	756.01	3.97
Aplastic anemia	327	19	5.8	725.15	26.2
Arrhythmia	1928	11	0.6	4262.3	2.58
Cellulitis	307	9	2.9	652.96	13.78
Dizziness	258	2	0.8	669.79	2.99
Vomiting	269	16	6	477.09	33.54
Dehydration	169	6	3.6	265.47	22.6
Pain	116	1	0.9	235	4.26
Headache	138	11	8	339.71	32.38
Bruising	74	1	1.4	150.43	6.65
Epistaxis	66	3	4.6	117.82	25.46
Fatigue	1497	38	2.5	3169.08	11.99
Petechiae	8	2	25	9.19	217.73
Autoimmune hemolytic anemia	38	2	5.3	72.07	27.75
Diseases of blood and blood- forming organs (below-mentioned diseases only)	4000	216	5.4	9036.81	23.9
Thrombocytopenia	1718	79	4.6	3660.59	21.58
Pancytopenia	1056	79	7.5	1990.68	39.68
Bone marrow failure	1351	89	6.6	2642.97	33.67
Neutropenia	730	67	9.2	1469.82	45.58
Blood disorder	642	46	7.2	1605.79	28.65
Leukopenia	410	30	7.3	1077.49	27.84
Leukocytosis	277	10	3.6	529.66	18.88
Lymphoma or Hodgkin's	372	36	9.7	715.08	50.34
disease[a]					
Lymphoma	352	34	9.7	674.16	50.43
Hodgkin's disease	26	2	7.7	48.34	41.38
Anemia	8255	206	2.5	21,190.87	9.72
Dyspnea/Shortness of breath	1355	25	1.9	2614.34	9.56
Lung disorder	830	24	2.9	1437.85	16.69
Diabetes mellitus (type 1 or type 2)	3405	38	1.1	8827.51	4.3

Patients with > 1 claim for allo-HSCT made ≥ 14 days apart were included in the analysis; patients with AML in the 6-month baseline (including index MDS date) were removed. The incidence event date was the date of the first claim for allo-HSCT. Allo-HSCT allogenic hematopoietic stem cell transplantation, AML acute myeloid leukemia, MDS myelodysplastic syndrome.

aTotal count of lymphoma or Hodgkin's disease does not equal the sum of separate lymphoma and Hodgkin's disease entries due to an overlap in patient population for both conditions.

Discussion

To date, MDS disease course-with its progression to AML or allo-HSCT-has been investigated in several studies with a small sample size. There have been only a few attempts at a population level to characterize clinical characteristics and to calculate the incidence of progression to AML or undergoing allo-HSCT in patients with MDS [7, 15-20]. In this study based on data from a large US-based healthcare claims database, the clinical course of patients with MDS who progressed to AML and of those who underwent allo-HSCT was characterized. Baseline factors associated with potential progression to AML or having an allo-HSCT were also investigated. Anemia (included as a co-morbid condition in this analysis) was among the most common co-morbidities observed at baseline, as expected in patients with MDS. We observed an IR of 18.7 per 1000 patients per year for progression of MDS to AML and two age peaks for the highest progression rates were noted (one in patients aged less than 18 years and another in those aged 50–69 years). It can be hypothesized that the increased IR in patients aged less than 18 years may be attributed to a different biology of the disease in the younger population, with particular germline mutations making these patients predisposed to progression from MDS to AML; however, such an analysis was beyond the scope of this study. The overall incidence rate of patients undergoing allo-HSCT after MDS diagnosis was as low as 10.2 per 1000 patients per year, with patients aged less than 18 years most likely to undergo the procedure. This was an expected finding, considering that allo-HSCT is often reserved for the fittest patients because of potential toxicities [10,12]. Younger patients tend to have a higher performance status and fewer co-morbidities, with lower non- relapse mortality (NRM) after allo-HSCT compared with older individuals. The probability of NRM tends to increase with age, in particular with high intensity (myeloablative) conditioning regimens, highlighting the need for careful assessment of both disease and patient characteristics before initiating allo-HSCT [21]. To date, several predictors of progression to AML in patients with MDS have been identified, including the presence of initiating gene mutations leading to clonal expansion, high percentage of marrow blasts, and infection at referral [22]. In this analysis, treatment with azacitidine was found to be the factor most significantly associated with progression of MDS to AML-an expected finding considering that the presence of higher-risk disease was likely to have been the reason for starting azacitidine. Azacitidine treatment was prominent both in patients with MDS who progressed to AML and in those who underwent allo-HSCT. Interestingly, many patients being treated with azacitidine for evolving AML went on to receive allo-HSCT. Despite being the only potentially curative option for MDS, the rate of allo-HSCT was low in this study. We observed that patients aged < 50 years and those aged 50 to 69 years were more likely to progress to AML than patients aged 70 to 79 years, indicating that age may be an important consideration in how aggressively patients are treated. Our observation reflected the findings from a recent study on prognostic features of secondary AML (defined as AML with an antecedent hematological disease or treatment-related AML), in which AML lacked prognostic value in the elderly patients [15]. Nevertheless, while age itself may not be a clear progression predictor, it is an important consideration when making treatment decisions as it influences other patient-related factors, such as performance status [12]. Currently, allo-HSCT is offered to only a small proportion of patients with MDS as illustrated by the findings of this study. We also observed that patients aged < 50 years were more likely to undergo allo-HSCT versus older patients. However, it has been shown previously that allo-HSCT provides an overall survival benefit in patients aged 60 to 70 years with intermediate- and high-risk MDS [18]. Additionally, allo-HSCT was an effective preventative measure against AML progression [22]. Moreover, an international expert panel recommended that fit patients with high- risk disease by IPSS-R should be considered for allo-HSCT regardless of age; patients with lower-risk disease by IPSS-R and with poor-risk genetic features, profound cytopenias, and high transfusion burden were also suggested as candidates for allo-HSCT [12]. As such, it is important to ensure that the eligibility criteria for patients with MDS considered for allo-HSCT in clinical practice reflect the current evidence as allo-HSCT may provide a valuable, life-saving option for many patients with MDS. There is some encouraging evidence that the number of allo-HSCT procedures is increasing. Based on data from the European Society for Blood and Marrow Transplantation, 940 patients with MDS underwent allo-HSCT in 2004, compared with 2646 in 2015 [23]. This increase is largely attributable to rising numbers of allo-HSCT procedures in older patients (> 60 years); this age cohort accounted for 22% of all transplants in 2004 but increased to 44% in 2015. In addition, there has been an increase in allo-HSCT from human leukocyte antigen (HLA)-matched unrelated donors, from 37% in 2004 to 58% in 2015 [23], and, most recently, in HLA-haploidentical donors [24]. Although determining the type of donors for allo-HSCT was not within the scope of this analysis, we also observed that allo-HSCT was performed in some older patients (> 60 years), but not in patients ≥ 80 years of age in our study. Our finding that patients who underwent allo-HSCT, versus those who did not, were more likely to have lymphoma is consistent with previous descriptions of MDS as a complication of lymphoma treatment [25-27]. Our study has a number of strengths. Firstly, the large sample size obtained from the Optum database allowed for an accurate evaluation of MDS-related claims. In addition, we were able to evaluate patients of all ages, rather than only the elderly ones, which makes the study findings more generalizable. The Optum database was selected as a data source as, in our view, it has a better representation of the Medicare population compared with other databases, such as PharMetrics or MarketScan®. Limitations should also be considered. The retrospective nature of the analysis comes with limitations common to similar studies conducted using administrative claims data. Some information in the claims sources was incomplete, such as duration of treatment with azacitidine and decitabine, and details on allo-HSCT. Also, there was no information

available regarding various MDS subtypes or genetics of the disease. Additionally, we believe there is an underestimation of blood transfusions reported in these data: the majority of patients with MDS are generally dependent on blood transfusions and the number of transfusions can be predictive of disease severity and poor prognosis [12,28]. Lastly, the duration of follow-up was short (median: 2.8 years), albeit similar to other published retrospective studies in MDS [29]. Nevertheless, we believe that this study provides valuable further information on the natural trajectory of the disease and factors associated with the decision-making process regarding allo-HSCT.

Conclusion

Overall, this analysis confirmed the heterogeneity of MDS. Baseline characteristics of the patients included in this analysis were investigated for their association with progression to AML and were largely consistent with those from previous studies [30]. With recent advances in our understanding of MDS and the introduction of novel techniques for allo-HSCT, it is important to reassess the eligibility criteria, since more patients than are currently offered the procedure may, in fact, be good candidates. As new medications to treat MDS-associated anemia are becoming available, this analysis could serve as a foundation for future larger studies to include assessment of the effect of new MDS medications on progression to AML or allo-HSCT.

Ethics approval and consent to participate

The study was conducted in accordance with the International Society for Pharmacoepidemiology guidelines for good pharmacoepidemiology practices [31], applicable regulatory requirements, and the 1964 Helsinki Declaration and its later amendments or comaparable ethical standards.

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Supplementary

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