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Comorbidities and survival in a large cohort of patients with newly diagnosed myelodysplastic syndromes

Rong Wang[a], Cary P. Gross[b], Stephanie Halene[c], Xiaomei Ma[a,*]

[a] Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT, United States
[b] Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, United States
[c] Section of Hematology, Yale University School of Medicine, New Haven, CT, United States

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ABSTRACT

Comorbid conditions have rarely been systematically studied among patients with myelodysplastic syndromes (MDS). We conducted a large population-based study to assess the role of comorbidity in the survival of newly diagnosed MDS patients. This study included 1708 MDS patients (age ≥ 66 years) diagnosed in the US during 2001–2002, with follow-up through the end of 2004. Hazard ratios (HRs) were estimated using multivariate Cox proportional hazard models. The median survival time was approximately 18 months. Fifty one percent of MDS patients had comorbid conditions. Patients with comorbid conditions had significantly greater risk of death than those without comorbidities. The HR was 1.19 (95% confidence interval (CI): 1.05–1.36) and 1.77 (95% CI: 1.50–2.08) for those with a Charlson index of 1–2 and ≥ 3, respectively. The risk of death increases with Charlson index. MDS patients who have congestive heart failure or chronic obstructive pulmonary disease had significantly shorter survival than patients without those conditions, whereas diabetes did not appear to have an impact on survival. This study confirms comorbidity as a significant and independent determinant of MDS survival, and the findings underscore the importance to take comorbid conditions into account when assessing the prognosis of MDS.

Myelodysplastic syndromes (MDS) are a group of clonal disorders characterized by ineffective hematopoiesis, cytopenia and frequent progression to acute myeloid leukemia (AML). MDS is most common among the elderly; the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) data show that approximately 80% of incident MDS patients are diagnosed at 65 years or older [1]. A few characteristics, such as age, gender, blast percentage, number of cytopenias, transfusion dependence and cytogenetics, have been linked to the survival of MDS patients [2,3].

Comorbidities, one or more diseases or disorders existed in addition to an index disease, are a significant concern among the elderly. In the U.S., 45% of the general population and 88% of the population aged 65 years or older have at least one chronic condition [4]. It has been reported that cancer patients 70 years or older have an average of three comorbidities [5]. Comorbidities may impact survival or treatment among cancer patients [6]. Studies have shown that comorbidities affect the prognosis of female breast cancer [7], head and neck cancer [8], and lung cancer [9]. In addition, comorbidities have been identified as significant determinants of response to therapy and survival in older patients with AML [10], a disease closely related to MDS.

Existing data on the role of comorbidities in the survival of MDS are scarce. Findings from two studies conducted in selected MDS patients suggest that comorbidities are useful in predicting survival of MDS patients after allogeneic stem cell transplantation [11] and MDS patients with supportive care only [12]. Another hospital-based study found that non-hematological comorbidities, such as cardiac diseases, liver or pulmonary disease and solid tumors, negatively affect the survival of MDS patients [13,14].

There is a paucity of large population-based studies on the prognostic role of comorbidities in MDS. A database linking records of the SEER program (which has included MDS since 2001) with Medicare claims (which can be used to assess comorbidities) provided a valuable framework for population-based studies to take place. Utilizing the unique SEER-Medicare database, we conducted this study to evaluate the prognostic role of comorbidities among a large cohort of newly diagnosed MDS patients.

1. Materials and methods

1.1. Data sources

The SEER program consists of population-based tumor registries in 17 geographic areas, which cover approximately 26.2% of the US population and include

* Corresponding author at: 60 College Street, Box 208034, New Haven, CT 06520-8034, United States. Tel.: +1 203 785 3880; fax: +1 203 785 6980.
E-mail address: xiaomei.ma@yale.edu (X. Ma).

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Table 1
Unadjusted and adjusted hazard ratios (and 95% confidence intervals) for selected demographic and clinical characteristics, SEER-Medicare, 2001–2002.

	Total		Censored	Dead	Univariate model			Multivariate model[a]		
Characteristic	*N*	%			HR	95% CI	*P* for trend	HR	95% CI	*P* for trend
Age (years)										
66–69	160	9.37	65	95	1.00		<0.01	1.00		<0.01
70–74	341	20.00	138	203	1.05	(0.82–1.34)		0.97	0.76–1.24	
75–79	406	23.80	148	258	1.15	(0.91–1.45)		1.17	0.93–1.49	
80–84	447	26.20	136	311	1.34	(1.06–1.68)		1.35	1.07–1.70	
85+	354	20.70	72	282	1.87	(1.48–2.37)		2.05	1.62–2.59	
Gender										
Female	812	47.50	294	518	1.00			1.00		
Male	896	52.50	265	631	1.17	(1.05–1.32)		1.16	1.03–1.30	
Race										
White	1527	89.40	495	1032	1.00					
Black	114	6.67	41	73	0.88	(0.70–1.12)				
Other	67	3.92	23	44	1.05	(0.77–1.42)				
Median household income										
1st Quartile	423	24.80	121	302	1.00		<0.01	1.00		<0.01
2nd Quartile	424	24.80	124	300	0.96	(0.82–1.13)		1.04	0.89–1.22	
3rd Quartile	421	24.70	141	280	0.85	(0.72–1.00)		0.92	0.78–1.08	
4th Quartile	422	24.70	166	256	0.74	(0.63–0.88)		0.84	0.71–0.99	
Charlson index										
0	840	49.20	314	526	1.00		<0.01	1.00		<0.01
1–2	619	36.20	201	418	1.19	(1.04–1.35)		1.19	1.05–1.36	
3+	249	14.60	44	205	1.73	(1.47–2.03)		1.77	1.50–2.08	
Urban/rural										
Big Metro	1002	58.70	333	669	1.00					
Metro	428	25.10	145	283	1.04	(0.90–1.19)				
Urban	88	5.15	29	59	1.01	(0.77–1.32)				
Less Urban	155	9.07	44	111	1.13	(0.92–1.38)				
Rural	35	2.05	8	27	1.25	(0.85–1.84)				
Subtype[b] (ICD-O-3 Code)										
RA (9980)	314	18.40	120	194	1.00			1.00		
RARS (9982)	203	11.90	113	90	0.63	(0.49–0.82)		0.66	0.51–0.84	
RAEB (9983)	237	13.90	25	212	2.26	(1.86–2.76)		2.47	2.02–3.01	
RCMD (9985)	54	3.16	24	30	1.00	(0.68–1.47)		1.07	0.73–1.58	
MDS, not otherwise specified (9989)	829	48.50	259	570	1.23	(1.05–1.45)		1.24	1.06–1.46	

[a] Age, gender, median household income, Charlson index and MDS subtypes are included in the model simultaneously.
[b] Results are not shown for subtypes with fewer than 50 patients.

the states of California, Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah, the metropolitan areas of Atlanta, Detroit and Seattle (Puget Sound), as well as rural Georgia and American Indians/Alaska Natives residing in the state of Alaska. Having long been viewed as pre-leukemic disorders, MDS are now considered malignancies due to the clonal nature. In the *International Classification of Diseases for Oncology, 3rd edition* (ICD-O-3) published in 2000, the behavior code for MDS was changed from "1" (uncertain whether benign or malignant) to "3" (malignant) [15]. In 2001, MDS became reportable to SEER.

The MDS histology types recorded in SEER are based on the ICD-O-3 codes, which overlap with both the French–American–British classification [16] and the World Health Organization recommendation [17,18]. Below is a list of the eight ICD-O-3 codes included in SEER for MDS: (1) 9980: refractory anemia (RA); (2) 9982: RA with ringed sideroblasts (RARS); (3) 9983: RA with excess blasts (RAEB, including RAEB under the FAB classification and both RAEB-1 and RAEB-2 under the WHO recommendation); (4) 9984: RAEB in transformation (RAEB-t); (5) 9985: refractory cytopenia with multilineage dysplasia (RCMD); (6) 9986: MDS associated with 5q deletion; (7) 9987: therapy-related MDS; and (8) 9989: MDS, not otherwise specified. Since the morphological feature of RAEB-t is considered more in line with that of AML, we conducted our analyses with and without the inclusion of patients with RAEB-t.

The linkage of the SEER data with the Medicare records is the collaborative effort of the NCI, the SEER registries, and the Center for Medicare and Medicaid Services (CMS). Among individuals who were included in SEER files and 65 years or older at the time of 1995 and 1999 linkages, 93% were found in the Medicare enrollment file [19]. In this study, we accessed Medicare claims from three sources: (1) the physician/supplier file, which contains claims for physician and other professional services; (2) the outpatient standard analytic file, which contains claims for outpatient facility services; and (3) the Medicare provider analysis and review file, which contains claims for hospital inpatient services.

1.2. Study population

All individuals with MDS between 2001 and 2002 were identified from the most recent linked database; their Medicare claims through the end of 2004 were also obtained. The subjects eligible to be included: (1) were 66 years or older at the time of diagnosis; (2) had Medicare Part A and Part B coverage and no health maintenance organization (HMO) enrollment during the period of interest, which begins 12 months before diagnosis and ends at the time of death or in December 2004, whichever was earlier; and (3) did not have other malignancies prior to the diagnosis of MDS. The rationale to limit the age of diagnosis to 66 years or older is to ensure a minimum of 12 months of Medicare claims prior to MDS diagnosis so comorbidities can be assessed [20,21]. We excluded patients who were enrolled in HMOs because their claims are not routinely reported to CMS [22]. Patients who had other malignancies prior to the diagnosis of MDS were excluded due to concern that their previous malignancies would affect survival and complicate the analysis. We also excluded patients who were identified from death certificates only and patients whose months of diagnosis were not specified. A total of 1708 incident MDS patients who were diagnosed during 2001–2002 and fulfilled the eligibility criteria were included in the analysis.

1.3. Study variables

Using claims record on inpatient, outpatient and carrier files from 1 year prior to the diagnosis of MDS through 1 month after the diagnosis, we calculated a summary measure of comorbid conditions known as the Charlson index [23]. First developed in 1987, the Charlson index is a summary measure of 19 comorbid conditions, each of which is assigned a weight from one to six corresponding to disease severity [19,23]. The weights are then summed to provide an overall score. To calculate this index, we used the Deyo adaptation with several procedure codes that reflect the Romano adaptation [24] (http://healthservices.cancer.gov/seermedicare/program/charlson.comorbidity.macro.txt). A total of 18 different conditions were included in this calculation, while cancer was not included (none of the patients included in our analysis had cancer prior to the diagnosis of MDS). We further grouped Charlson index into three categories, 0, 1–2 and 3+.

In addition to comorbid conditions, we obtained information on demographic characteristics and neighborhood socioeconomic status (SES) from the database. The database includes aggregate socioeconomic measures from the US Census Bureau