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Derivation and Validation of the SEER-Medicare Myelodysplastic Syndromes Risk Score

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Abstract

Accruing data since 2001, the SEER-Medicare dataset is an outstanding resource for MDS-related comparative effectiveness research; however, although several MDS prognostic models exist, complete data required to calculate them are not available therein. Using SEER-Medicare as a training and internal validation set (n=9820) and clinical data at our institution as an external validation set (n=307), we created a new MDS risk score (the SMMRS) for use with SEER-Medicare. Risk stratification by the SMMRS was comparable to the IPSS (net reclassification improvement index was 0.0), demonstrating that it is a useful research tool to stratify MDS patients in studies using SEER-Medicare.

Keywords

MDS; SEER; SEER-Medicare; prognosis; comparative effectiveness

1. Introduction

The myelodysplastic syndromes (MDS), hematopoietic stem cell disorders that primarily affect the elderly, are one of the most common myeloid malignancies according to Surveillance Epidemiology and End Results (SEER) data.¹⁻³ The syndromes can be devastating, as patients who do not succumb to infections or bleeding may develop acute myeloid leukemia. Until the last decade, MDS was managed primarily with supportive care and blood transfusions, but in the mid 2000's, three medications were approved by the Food

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Contributions

All authors collected (HU, MW, GA) or analyzed (HU, AC, DS, GA) the data, and all authors (HU, AC, MW, DS, and GA) wrote and approved the manuscript.

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and Drug Administration for patients with these diseases: azacitidine,^{4,5} lenalidomide,⁶ and decitabine;^{7,8} another, deferasirox, is now sometimes used for managing secondary hemosiderosis in transfusion-dependent MDS patients.⁹

Although these agents have been shown to benefit patients in terms of disease progression, transfusion dependence, iron overload, and even survival, these findings were based on modest-sized clinical trials of patients who were free of significant comorbid illness. As a consequence, despite these advances for a hitherto largely untreatable condition, little is known about the best approach for MDS patients in the “real world” of clinical practice. Such uncertainty is the ideal setting for observational comparative effectiveness research (CER).

Fortunately, MDS became reportable to the SEER Program of the National Cancer Institute in 2001, and these data are maturing. After standard exclusions, there are well over 14,000 cases in the current release (2001-2009). On the other hand, unlike solid tumors, where disease risk roughly correlates with stage at diagnosis, disease risk for MDS patients focuses on many clinical factors that are not captured in SEER, or even surmisable when linked to claims (SEER-Medicare). These factors (such as baseline cytogenetics and number of blasts) are used in models such as the International Prognostic Scoring System (IPSS)¹⁰ and its revision (IPSS-R),¹¹ the WHO Prognostic Scoring System (WPSS),¹² and the MD Anderson Cancer Center MDS Model (MDACC)¹³ to predict baseline disease risk; however, no model in its entirety can be calculated with SEER-Medicare data alone. We thus aimed to create a completely claims-based prognostic scoring system to facilitate MDS-related CER for SEER-Medicare: the SEER-Medicare MDS Risk Score (SMMRS).

2. Materials and Methods

Dataset

We used the 2001-2007 SEER-Medicare MDS dataset (n=9820 after standard exclusions, including CMML and MDS/MPD overlap syndromes) as a derivation set, and an MDS clinical database at Dana-Farber Cancer Institute (the DFCI/MDS CRIS database, consisting of consecutive MDS patients followed at DFCI since 2006, with over 90% enrollment; n=307) as an independent validation set (importantly, DFCI is not a SEER institution). We used the DFCI/MDS CRIS database to compare the performance of the claims-based model we derived with that of the IPSS, as the DFCI/MDS CRIS database contains information from abstracted medical records including laboratory and pathology values that are required for calculating the existing MDS prognostic scores.

Model Derivation

Using 2001-2007 SEER-Medicare data, we derived a Cox proportional hazards model with overall survival as the outcome variable. Borrowing from the three MDS risk scoring systems listed above, a set of candidate predictors that could be ascertained from Medicare claims in a window close to diagnosis was pre-specified. This consisted of cytopenias, MDS pathologic category, age at diagnosis, Charlson comorbidity score, presence of acute hospitalizations, and red blood cell and/or platelet transfusion dependence. MDS *pathologic*

category was taken from SEER (CMML and MDS/MPD were excluded). For *cytopenias* (i.e., anemia, neutropenia, thrombocytopenia, and pancytopenia), we used ICD-9 diagnosis codes occurring within two months prior to or post diagnosis. We used HCPCS codes, and/or ICD-9 procedure code codes to identify presence of *red blood cell or platelet transfusions*. Red cell or platelet *transfusion dependence* was defined as more than one claim for transfusion within two months prior to or post diagnosis. For *hospital admissions*, we included inpatient claims for acute hospital care within two months prior to or post diagnosis. For more precise definitions with associated claims codes, please see the Appendix.

The functional form of each factor was determined empirically. Specifically, for the categorical variables with more than 2 levels (i.e., cytopenia, MDS classification, red cell transfusion, platelet transfusion), we first estimated the hazard ratio of each category, using dummy variables in Cox proportional hazards models. We then collapsed several categories, if it seemed clinically reasonable to put those categories together and the hazard ratio estimates were also similar to each other. Categories with small cell probabilities were also absorbed into larger clinically appropriate categories during this process. The quantitative variables (i.e., age, Charlson comorbidity index) were used as a single continuous variable since the linear association appeared to be reasonable. The SMMRS was derived as a linear combination of these predictors; the contribution of each factor was determined by the regression coefficient of the final Cox regression model (Table 1). Three-year predicted mortality was determined by a simple transformation of the SMMRS. Specifically, let $\Lambda(t = \Lambda_0(t)\exp(\text{SMMRS}))$ denote the cumulative hazard function, at month t , for a patient with a SMMRS score, where $\Lambda_0(t)$ is the estimated baseline cumulative hazard function estimated by the Breslow method. Since, at Year 3 (i.e., $t = 36$ months), $\Lambda_0(36)$ was 0.025, we calculated three-year predicted mortality for each patient by $1 - \exp\{-0.025 \times \exp(\text{SMMRS})\}$, based on the patient's SMMRS.

Model Validation

To assess the performance of the SMMRS, we calculated C-statistics with both the derivation set (the SEER-Medicare data) and the validation set (the DFCI/MDS CRIS data), censoring survival at 36 months after diagnosis.¹⁴ For the internal validation using the SEER- Medicare data, we used a random cross-validation procedure in estimating C-statistics. Specifically, we randomly split the data into two sets. We used one set to estimate the model parameters, and then applied it to the other set and calculated C-statistics. We repeated this process 100 times and took averages of 100 estimates of C-statistics.

The DF/MDS CRIS data served as an external validation dataset to assess the robustness of the SMMRS. Survival time was defined from the date of diagnosis through date of death or date of last follow up. We used information at initial MDS diagnosis for WHO classification, and at first presentation to DFCI for the remaining variables (comorbidity, marrow blasts, cytogenetic results, hemoglobin, ANC, and platelet levels). Hematocrit levels were used in the absence of hemoglobin levels (divided by 3); marrow blasts and cytogenetic results at initial MDS diagnosis were used in the absence of those at DFCI

presentation. Hospitalizations were assessed relative to initial MDS diagnosis. Table 1 describes the distribution of the predictors of the SMMRS with this cohort.

We calculated C-statistics for the SMMRS in the DF/MDS CRIS data in two ways. We first followed the current common analytical practice of most validation studies, where performance indices are estimated by simply applying a model to a validation set. Next, we calculated what we call an “adjusted C,” where the distribution of the risk score in the validation cohort is adjusted to that of the derivation cohort. As Table 1 shows, the distribution of the predictors in the DF/MDS CRIS cohort was rather different from the SEER-Medicare data. In such a situation, an “adjusted C” provides important insight regarding the validity of the prediction model, because the C-statistic depends on the distribution of the risk score.

We employed a probability ratio weighting approach to calculate the adjusted C. We grouped patients in the SEER-Medicare dataset into 4 groups, based on their SMMRS, where we used the quartile of the score distribution as the cutoffs. Patients from the DF/MDS CRIS data were also grouped into 4 categories, using the same cutoff values. Of note, the proportion of subjects in each category is 25% in the SEER-Medicare dataset by definition, but it was not necessary to be 25% in the DF/MDS CRIS dataset. We then calculated the ratio (SEER-Medicare vs. DF/MDS CRIS) of the cell probabilities for each stratum, which was used, when calculating C-statistics, as a weight for each patient in the corresponding stratum.

Comparison with IPSS Risk Stratification

Using the DF/MDS CRIS data, we next assessed how SMMRS-based risk stratification using four categories based on SMMRS three-year predicted mortality score—we determined these cutoff values so that the number of patients in each risk group was matched to the number of patients in the corresponding IPSS prognostic group—compared to the four categories of the IPSS in terms of median survival times. We then calculated a net reclassification improvement index (NRI)¹⁵ for the two models (SMMRS and IPSS) in the DFCI/MDS CRIS data. Note that, of the 307 patients, 25 with unknown IPSS values due to missing component data were excluded from this analysis, leaving 282 patients. All analyses were performed using SAS (version 9.2, Cary, NC), Stata (version 12.1, College Station, Texas), and R (version 3.1, The Comprehensive R Archive Network).

3. Results and Discussion

In the final SMMRS model, for the training set, we obtained a C statistic of 0.690, suggesting relatively good predictive performance. We then applied the SMMRS to the validation dataset and obtained $C = 0.649$ (unadjusted) and 0.650 (adjusted), also significantly better than chance at predicting three-year survival. SMMRS-based risk stratification also did well when compared to the IPSS prognostic groups (Low, Intermediate-1, Intermediate-2, and High) using the DFCI/MDS CRIS data set. For the SMMRS, patients were grouped into four risk categories as described above, with 25 patients with unknown IPSS scores excluded from the analysis. The SMMRS three-year predicted mortality scores were as follows: Low (SMMRS score 0.28), Intermediate-1

(>0.28 to 0.50), Intermediate-2 (>0.50 to 0.69) and High (>0.69). Median survival times by the IPSS prognostic groups were 53.1 (Low), 34.8 (Intermediate-1), 21.8 (Intermediate-2) and 17.8 months (High); the counterparts with the SMMRS were 54.0, 36.9, 24.9, and 15.1 months, respectively.

Figure 1 shows the Kaplan-Meier curves for SMMRS and the IPSS in the DFCI/MDS CRIS data. No significant differences were seen between the two systems after stratifying for risk category. The predictive performance of the SMMRS-based risk classification ($C=0.63$) was comparable to that of the IPSS ($C=0.64$). The net reclassification improvement index (NRI)¹⁵ for the two models was 0.00 [-0.22-0.23], indicating that no significant difference in predictive performance was observed between the two risk categorization systems (see Table 2). Finally, a second analysis restricting the DFCI/MDS CRIS data to those patients 65 and older to more closely follow the SEER-Medicare population yielded similar results (data not shown).

While we found that the SMMRS has similar predictive value to the IPSS and is potentially useful for observational CER using SEER-Medicare, it is important to note that the SMMRS is tailored for SEER-Medicare and so does not take cytogenetics, molecular markers,¹⁷ or percentage of marrow blasts into account (the last only indirectly through morphologic subtype). We acknowledge that it is not for clinical use, and only for use in research with the SEER-Medicare dataset. Indeed, while our analyses show that it can be used to determine how treatments perform in different MDS risk groups in observational analyses, we do not suggest that SEER-Medicare analyses using the SMMRS can replace clinical trials stratifying patients with well-validated biologically-oriented existing MDS models.

We also acknowledge several limitations to our work. First, the revised IPSS is coming into wider clinical use; our score has only been tested with the IPSS, and it would likely perform less well given the more granular clinical information required to calculate the revised version. Unfortunately, our validation set was not large enough to assess the similarity between SMMRS-based stratification and IPSS-R based stratification across the 5 categories of the IPSS-R. Further investigation will be warranted as our DF/MDS CRIS dataset grows. Second, the SMMRS is only useful for assessing baseline risk, as it is not dynamic (although neither is the IPSS or IPSS-R). We also acknowledge that the SMMRS does not take into account the effect of any treatments after diagnosis. However, we did not observe that year of diagnosis (i.e., as a surrogate of the approval of newer agents) affected the three-year overall survival in the SEER-Medicare data (up to 2007, our study end date), and the IPSS does not take treatment into account either. Finally, billing for cytopenias after MDS diagnosis could be due to therapy effect (rather than baseline disease), resulting in an overestimation of risk; however, we aimed to ameliorate this issue by limiting our codes to those found only in the two months before or after diagnosis, when treatment effects are less likely to appear.

4. Conclusions

In summary, the SMMRS is a valid MDS prognostic scoring system for research using SEER-Medicare data. We intend the SMMRS to be a public resource, and the code to

calculate it is available upon request. Although missing some important clinical characteristics that cannot be ascertained from claims (eg, cytogenetics, molecular markers), the SMMRS can risk-stratify SEER-Medicare MDS patients with a precision similar to that of the IPSS, a risk model that was the gold standard for at least 15 years and still in wide clinical use. While the SMMRS is not an alternative to existing well-validated clinical risk classification systems for MDS patients, it is a useful tool for observational research with SEER-Medicare. Specifically, it can help address one of the weaknesses of CER analyses that use observational data, which is the potential impact of confounding due to baseline disease risk.¹⁶ Indeed, as determination of such baseline risk is key to any MDS analysis, it is a new resource that promises to better evaluate the impact of alternative treatments for MDS patients.

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Appendix

Appendix

Codes used to derive variables from Medicare claims files

Variable	Code type	Code	Time period
Anemia	ICD-9 Diagnosis	280.0, 280.1, 280.8, 280.9, 281, 281.0, 281.2, 281.3, 282, 282.0, 283.2, 284, 284.0, 284.01, 284.09, 284.1, 284.8, 284.81, 284.89, 284.9, 285, 285.0, 285.2, 285.21, 285.22, 285.29, 285.3, 285.8, 285.9	Diagnosis $\pm$ 2 months
Thrombocytopenia	ICD-9 Diagnosis	287.5x, 287.4, 287.3x	Diagnosis $\pm$ 2 months
Neutropenia	ICD-9 Diagnosis	288.0x, 288.5x, 288.9, 288.8	Diagnosis $\pm$ 2 months
Pancytopenia	ICD-9 Diagnosis	284.1 OR presence of all 3 above (anemia, thrombocytopenia, and neutropenia)	Diagnosis $\pm$ 2 months
Red Blood Cell transfusion	ICD-9 Procedure	99.03, 99.04	(see below)
	HCPCS	C9504, C9505, P9010, P9011, P9016, P9021, P9022, P9038, P9039, P9040, P9051, P9054, P9056, P9057, P9058	
	Revenue center	0381, 0382	
Platelet transfusion	HCPCS	C9500, C9501, C9502, P9019, P9020, P9031, P9032, P9033, P9034, P9035, P9036, P9037, P9052, P9053, P9055	(see below)
	Revenue center	0384	
Red Blood Cell transfusion dependence	n/a	2 claims for red blood cell transfusion	Diagnosis $\pm$ 2 months

Variable	Code type	Code	Time period
Platelet transfusion dependence	n/a	2 claims for platelet transfusion	Diagnosis $\pm$ 2 months
Prior history of Red Blood Cell transfusion	n/a	1 claim for red blood cell transfusion	Diagnosis - 12 months
Prior history of platelet transfusion	n/a	1 claim for platelet transfusion	Diagnosis - 12 months

• For variables in Table 1, the following Medicare claims files were used: durable medical equipment, home health, hospice, carrier (AKA NCH), inpatient (AKA Medpar), and outpatient.

• For hospital admissions, we included inpatient claims corresponding with acute hospital care, after exclusion of claims for skilled nursing facilities. The time window was also 'diagnosis $\pm$ 2 months'.

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Highlights

- SEER-Medicare is an outstanding resource for MDS-related observational research.
- Complete data to calculate standard prognostic models are not available therein.
- We created an MDS risk scoring system (the SMMRS) for use with SEER-Medicare.
- The predictive performance of the SMMRS appears to be comparable to the IPSS.
- The SMMRS is not an alternative to the IPSS for clinical use, but a research tool.

A. Stratification by SMMRS

B. Stratification by IPSS

Figure 1.

Overall Survival by Risk Score with DFCI CRIS Data (NB: Kaplan-Meier curves for low risk (red), intermediate-1 (orange), intermediate-2 (green), and high (blue) by each stratification system)

Table 1

Distribution of SMMRS Components in SEER-Medicare and DFCI/MDS CRIS

	SEER-Medicare N=9820	DFCI/MDS CRIS N=307	Contribution to SMMRS
Cytopenias			
Anemia only or absence of anemia	4640 (47)	157 (51)	0
Anemia + Neutropenia	1660 (17)	15 (5)	+0.11
Anemia + Thrombocytopenia	1636 (17)	102 (33)	+0.31
Anemia + Neutropenia + Thrombocytopenia	1884 (19)	33 (11)	+0.39
MDS category *			
RA or 5q-	1713 (17)	21 (7)	0
RAEB, RAEB-t, RCMD, tMDS	2008 (20)	195 (64)	+0.61
RARS	1059 (11)	17 (6)	-0.08
MDS NOS	5040 (51)	74 (24)	+0.23
Age at diagnosis (years)			
			+0.04 × (age)
Mean (SD)	80 (6.8)	66 (11.6)	
Range	66 to 107	19 to 90	
18-65	0 (0)	135 (44)	
66-70	804 (8)	60 (20)	
71-75	1638 (17)	46 (15)	
76-80	2406 (25)	40 (13)	
81-85	2624 (27)	20 (7)	
>85	2348 (24)	6 (2)	
Charlson comorbidity index; CCI **			
			+0.08 * (CCI)
Mean (SD)	2.4 (2.1)	1.4 (1.7)	
Range	0 to 13	0 to 12	
0	2185 (22)	136 (44)	
1	1582 (16)	44 (14)	
2	1932 (20)	67 (22)	
3	1517 (15)	35 (11)	
4+	2604 (27)	25 (8)	
Acute hospitalization			
No	4502 (46)	267 (87)	0
Yes	5318 (54)	40 (13)	+0.46
RBC/PLT transfusion			
No dependency	7155 (73)	216 (70)	0
Transfusion dependent: either RBC or PLT	2437 (25)	74 (24)	+0.57
Transfusion dependent: both RBC and PLT	228 (2)	17 (6)	+0.87

* CMML cases were excluded.

** An index score greater than 6 is replaced by 6.

Table 2

Reclassification Table Comparing IPSS and SMMRS Risk Categorization for 3-Year Mortality Risk

IPSS	SMMRS risk categorization				Total, n (%)	Reclassified into new category, %		
	Low	Intermediate-1	Intermediate-2	High		Lower	Higher	Total
Low								
Patients included, n(%)	10 (25.6)	20 (51.3)	6 (15.4)	3 (7.7)	39 (13.8)	--	74.4	74.4
Death by Year-3, n(%)	2 (33.3)	2 (33.3)	1 (16.7)	1 (16.7)	6 (4.6)	--	66.7	66.7
Survive at Year-3, n(%)	3 (20.0)	9 (60.0)	2 (13.3)	1 (6.7)	15 (21.7)	--	80.0	80.0
Intermediate-1								
Patients included, n(%)	17 (15.6)	45 (41.3)	28 (25.7)	19 (17.4)	109 (38.7)	15.6	43.1	58.7
Death by Year-3, n(%)	3 (6.7)	20 (44.4)	11 (24.4)	11 (24.4)	45 (34.4)	6.7	48.9	55.6
Survive at Year-3, n(%)	5 (18.5)	13 (48.1)	8 (29.6)	1 (3.7)	27 (39.1)	18.5	33.3	51.9
Intermediate-2								
Patients included, n(%)	9 (10.6)	26 (30.6)	33 (38.8)	17 (20.0)	85 (30.1)	41.2	20.0	61.2
Death by Year-3, n(%)	2 (4.2)	14 (29.2)	18 (37.5)	14 (29.2)	48 (36.6)	33.3	29.2	62.5
Survive at Year-3, n(%)	6 (35.3)	6 (35.3)	4 (23.5)	1 (5.9)	17 (24.6)	70.6	5.9	76.5
High								
Patients included, n(%)	3 (6.1)	18 (36.7)	18 (36.7)	10 (20.4)	49 (17.4)	79.6	--	79.6
Death by Year-3, n(%)	0 (0.0)	10 (31.3)	13 (40.6)	9 (28.1)	32 (24.4)	71.9	--	71.9
Survive at Year-3, n(%)	3 (30.0)	5 (50.0)	2 (20.0)	0 (0.0)	10 (14.5)	100.0	--	100.0
Total								
Patients included, n(%)	39 (13.8)	109 (38.7)	85 (30.1)	49 (17.4)	282 (100.0)			
Death by Year-3, n(%)	7 (5.3)	46 (35.1)	43 (32.8)	35 (26.7)	131 (100.0)			
Survive at Year-3, n(%)	17 (24.6)	33 (47.8)	16 (23.2)	3 (4.3)	69 (100.0)			

Probability(UP | Death by Year-3)=0.314

Probability(Down| Death by Year-3)=0.305

Probability(UP | Survive at Year-3)=0.345

Probability(Down | Survive at Year-3)=0.350

NRI=(0.314- 0.305) + (0.345 - 0.350)=0.004