The efficacy of current prognostic models in predicting outcome of patients with myelodysplastic syndromes at the time of hypomethylating agent failure

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Statistical Methods:

Missing data were multiply imputed using the chained equation approach with 10 iterations per variable as implemented in the R package mice (1). Random forest imputation using bootstrap resampling and 500 trees was used for both continuous and categorical variable imputation within the chained equation approach (2). The fraction of missing information (fmi), which represents the impact missing data have on the quantity of interest, was also estimated, summarized in supplementary Table 4. When models were applied at diagnosis, survival was calculated from diagnosis to death or last follow up and from the date of HMA failure until date of death or last known follow-up when models were applied at the time of HMA failure. To generate a new prognostic model at HMA failure, 23 variables were considered (supplemental data Table 1), including clinical variables, treatment history and demographics. We used the multivariable fractional polynomial (MFP) procedure assuming an additive Cox proportional hazards (CPH) model within each multiply dataset for prediction model development(3, 4). To assess the stability and the internal performance of our prediction models, we used bootstrap re-sampling(5). A total of 200 bootstrap samples with replacement of subject ids were chosen. Predictor inclusion and transformations were recorded for each sample and averaged across samples to get an overall inclusion percentage. Predictors that were selected in at least 70% of the bootstrap samples were considered to be stable.

References

1. Buuren SV G-OKmMIbCEiRJSS-, 2011.
2. Shah AD, Bartlett JW, Carpenter J, Nicholas O, Hemingway H. Comparison of random forest and parametric imputation models for imputing missing data using MICE: a CALIBER study. American journal of epidemiology. 2014 Mar 15;179(6):764-74.
3. Royston P SWMm-bapatrabofpfmcvVJWS, 2008.
4. Vergouwe Y, Royston P, Moons KG, Altman DG. Development and validation of a prediction model with missing predictor data: a practical approach. Journal of clinical epidemiology. 2010 Feb;63(2):205-14.
5. Moons KG, Kengne AP, Woodward M, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart (British Cardiac Society). 2012 May;98(9):683-90.

Supplementary Table 1: Patient characteristics at diagnosis

Parameter	No.	%
Total	455	
Median age, years Range	70 30 - 91	
Gender		
Male	304	68
Female	146	32
Clinical Characteristics		
Median white blood cell count $x10^9$/L Range	2.7 .5 - 77.1	
Median hemoglobin, g/dl Range	9.3 3.1 - 15.2	
Median absolute neutrophil count $x10^9$/L Range	1.4 .02 - 45	
Median platelet $x10^3$/mL Range	67 3 - 661	
Median bone marrow blast % Range	12 0 - 29	
Bone marrow blast %		
< 5%	62	14
>= 5% & < 10%	114	25
>= 10% & < 20%	250	55
>= 20%	29	6
WHO classifications		
RCUD	14	3
RCMD	47	10
RARS	8	2
RAEB-1	121	26
RAEB-2	259	57
MDS-U	5	1
MDS del(5q)	1	1
FAB classifications		
RA	22	5
RARS	12	3
RAEB	303	67
RAEB-T	48	11
Missing	70	15
Secondary MDS	111	24

Abbreviations: WHO = World Health Organization, FAB = French–American–British, RCUD = refractory cytopenia with unilineage dysplasia, RCMD = refractory cytopenia with multilineage dysplasia, RARS = refractory anemia with ring sideroblasts, RAEB = refractory anemia with excess blasts, RA = refractory anemia, RAEB-T = refractory anemia with excess blasts-transformation, CMML = chronic myelomonocytic leukemia.

Supplementary Table 2: Clinical variables included at the time of hypomethylating agent (HMA) failure

Clinical variables
Age at diagnosis
Age at the time of HMA failure
Gender: male vs female
Race: white vs others
ECOG performance status at the time of HMA failure
White blood cell count at the time of HMA failure
Absolute neutrophil count at the time of HMA failure
Hemoglobin at the time of HMA failure
Platelets count at the time of HMA failure
Peripheral blood blasts percentage at the time of HMA failure
Bone marrow blasts percentage at the time of HMA failure
Cytogenetic categories per IPSS at the time of HMA failure
Cytogenetic categories per IPSS-R at the time of HMA failure
Transfusion dependency at diagnosis
Platelets transfusion dependency at the time of HMA failure
Red blood cell transfusion dependency at the time of HMA failure
Transfusion dependency at the time of HMA failure
Number of prior lines of therapies
Time from start therapy to best response
Time from diagnosis to start therapy
Duration of HMA treatment
Best response to HMA
Treatment with azacitidine vs decitabine

Supplementary Table 3: AICc for post HMA model compared to current models when risk groups were combined into lower versus higher risk

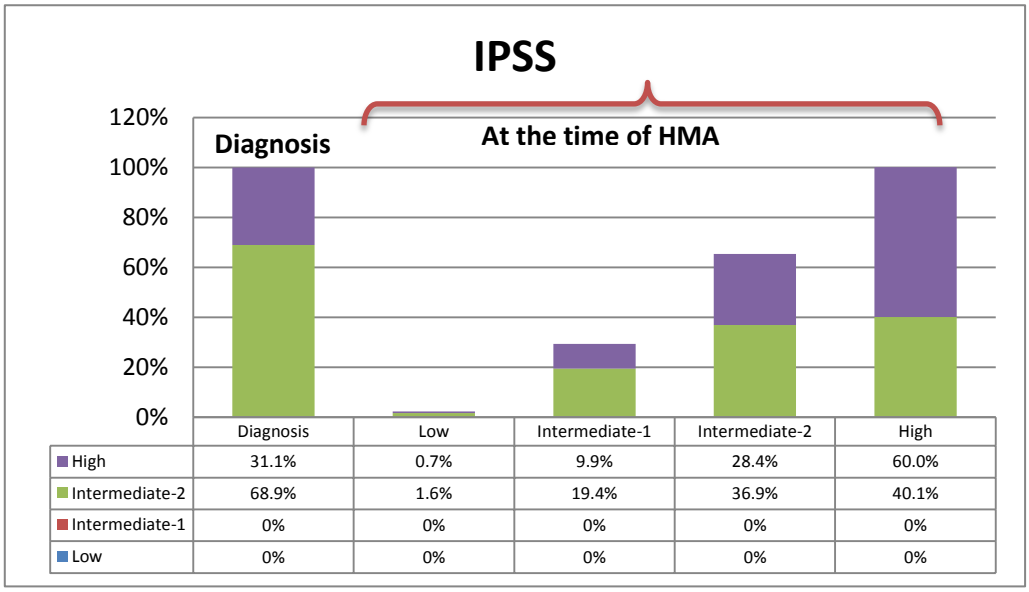
Prognostic System	AICc
Post HMA Model	3500.3
MDAPSS	3541.9
IPSS-R	3562.1
IPSS	3572.3
WPSS	3573.4

Supplementary Table 4: Fraction of missing data at diagnosis and at the time of hypomethylating agent failure

Variable	FMI
Age at diagnosis	0.22
Age at HMA failure	3.08
Gender	0
WBC at diagnosis	5.73
WBC at HMA failure	25.77
ANC at diagnosis	9.69
ANC at HMA failure	30.62
Hb at HMA diagnosis	5.95
Hb at HMA failure	25.77
Platelets at diagnosis	5.29
Platelets at HMA failure	25.99
Bone marrow blasts percentage at diagnosis	3.52
Bone marrow blasts percentage at HMA failure	30.84
Cytogenetic per IPSS criteria at diagnosis	7.05
Cytogenetic per IPSS-R criteria at diagnosis	7.05
Cytogenetic per MDAPSS criteria at diagnosis	7.05
Cytogenetic per IPSS criteria at HMA failure	35.46
Cytogenetic per IPSS-R criteria at HMA failure	35.46
Cytogenetic per MDAPSS criteria at HMA failure	35.46
ECOG performance status at diagnosis	
ECOG performance status at the time of HMA failure	34.58
Transfusion dependency for platelets at diagnosis	39.21
Transfusion dependency for red cells at diagnosis	38.33
Transfusion dependency for platelets at HMA failure	46.48
Transfusion dependency for red cells at HMA failure	45.59
Time from start therapy to best response	14.1
Time from diagnosis to start HMA	0.44

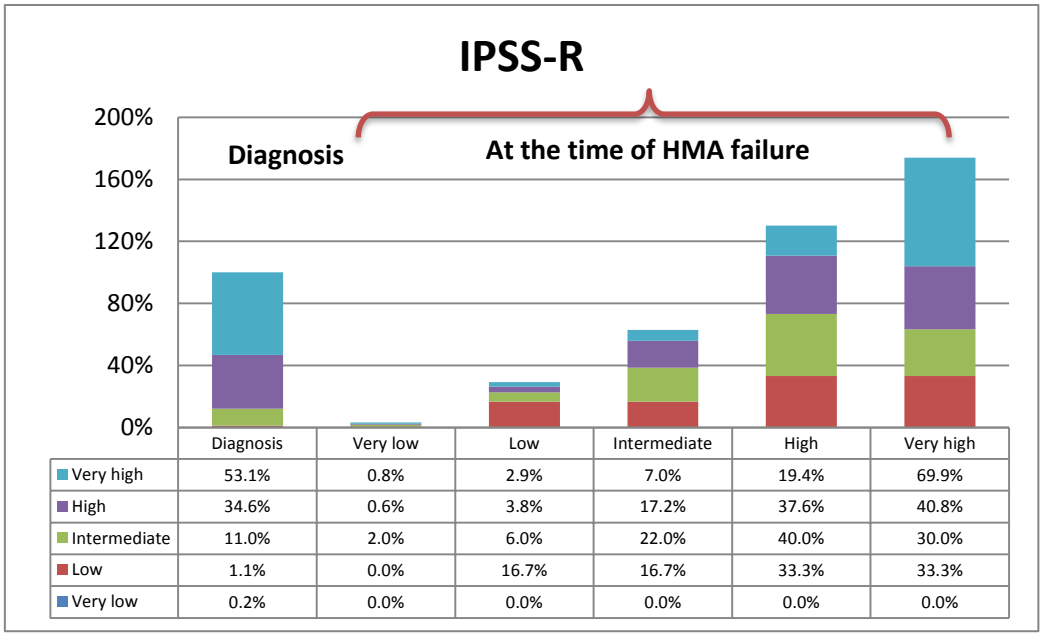
Figure1: Distribution of patients by each scoring system at diagnosis and at the time of hypomethylating agents

(A)



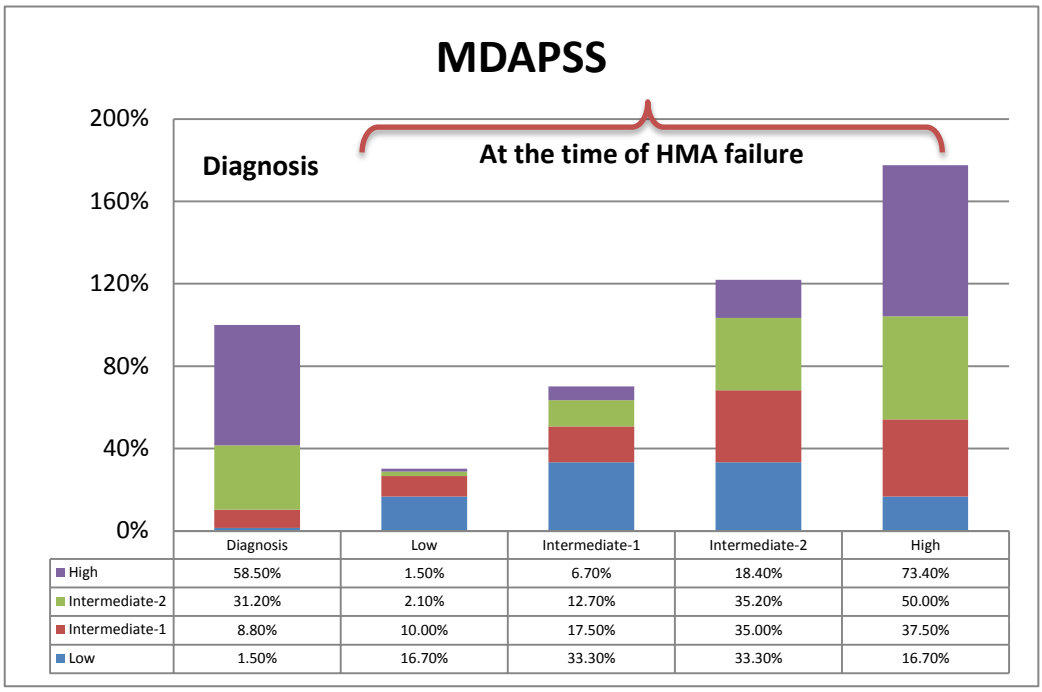
	Diagnosis	Low	Intermediate-1	Intermediate-2	High
High	31.1%	0.7%	9.9%	28.4%	60.0%
Intermediate-2	68.9%	1.6%	19.4%	36.9%	40.1%
Intermediate-1	0%	0%	0%	0%	0%
Low	0%	0%	0%	0%	0%

(B)



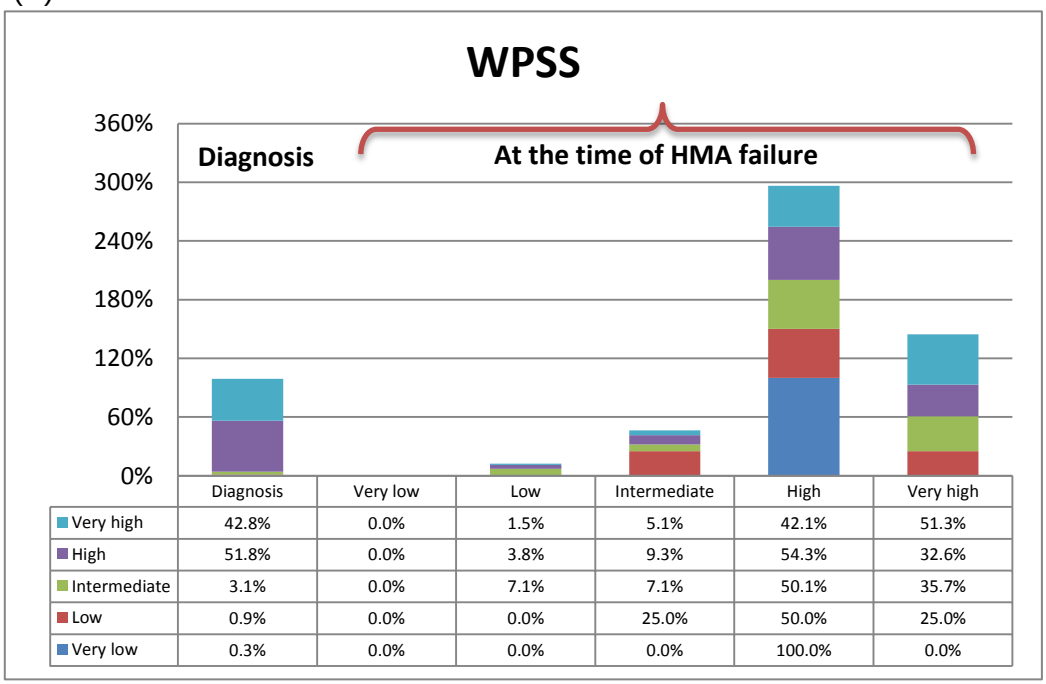
	Diagnosis	Very low	Low	Intermediate	High	Very high
Very high	53.1%	0.8%	2.9%	7.0%	19.4%	69.9%
High	34.6%	0.6%	3.8%	17.2%	37.6%	40.8%
Intermediate	11.0%	2.0%	6.0%	22.0%	40.0%	30.0%
Low	1.1%	0.0%	16.7%	16.7%	33.3%	33.3%
Very low	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%

(C)



	Diagnosis	Low	Intermediate-1	Intermediate-2	High
High	58.50%	1.50%	6.70%	18.40%	73.40%
Intermediate-2	31.20%	2.10%	12.70%	35.20%	50.00%
Intermediate-1	8.80%	10.00%	17.50%	35.00%	37.50%
Low	1.50%	16.70%	33.30%	33.30%	16.70%

(D)



	Diagnosis	Very low	Low	Intermediate	High	Very high
Very high	42.8%	0.0%	1.5%	5.1%	42.1%	51.3%
High	51.8%	0.0%	3.8%	9.3%	54.3%	32.6%
Intermediate	3.1%	0.0%	7.1%	7.1%	50.1%	35.7%
Low	0.9%	0.0%	0.0%	25.0%	50.0%	25.0%
Very low	0.3%	0.0%	0.0%	0.0%	100.0%	0.0%

Abbreviations: IPSS = International Prognostic Scoring System, IPSS-R = Revised IPSS, MDAPSS = MD Anderson Prognostic Scoring System, WPSS = World Health Organization classification-based Prognostic Scoring System