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Letter to the Editor

The World Health Organisation classification of myelodysplastic syndromes contains prognostically relevant information beyond the prognostic scores IPSS-R or WPSS

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Dear Sir,

In their interesting retrospective study, van Spronsen *et al.* [1] compared the prognostic relevance of the FAB and WHO classifications with the IPSS-R score in MDS patients and concluded that the morphological classification models were of no prognostic relevance beyond the revised International Prognostic Score System (IPSS-R). The authors performed survival analyses with Kaplan–Meier-plots, log-rank tests and multivariate Cox regressions, to examine whether morphological classification models could add prognostic value to IPSS-R. However, some methodological details are missing in their paper. Most probably they have used stepwise selection procedures for the multivariate Cox analyses. Since the user can choose among several variable selection algorithms in the SPSS program, different final models may be created. Moreover, very small statistical fluctuations of the data could be relevant for the choice of the final Cox model. In the light of these methodological uncertainties, and the provoking suggestion to stop the use of morphological classification models for MDS risk stratification, we decided to reanalyse our own data of 101 MDS patients [2–5]. In this prospective cohort, only patients with high risk disease had been treated by cytotoxic therapy. All other patients had received only supportive care. Patients with chemotherapy or BM transplantation had been censored at beginning of the treatment.

First, we calculated univariate Cox models for overall survival until May 2016, stratifying according to FAB, WHO, IPSS-R or WHO classification-based Prognostic Score System (WPSS). In multivariate Cox regressions, we compared the following pairwise combinations: WHO/IPSS-R, WHO/WPSS, FAB/IPSS-R and FAB/WPSS using the backward selection algorithm ($p = 0.05$ for inclusion and $p = 0.10$ for exclusion). The Akaike information criterion (AIC) and its relative weight (w), both based on the maximised log-likelihood and the number of parameters in the Cox regressions, were calculated to estimate the discriminatory power of these models and their relative goodness-of-fit regarding the overall survival curve [3,4]. Lower AIC or higher w values are equivalent to better explanatory power of the model. The internal stability was evaluated by bootstrap resampling, where 100 new data sets with identical sample size were created by random sampling from the pool of original data with replacement. Then, Cox

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Table 1
Akaike information criteria derived from variables regarding overall survival for MDS classifications and their combinations regarding original data.

	FAB	WHO	IPSS-R	WPSS	WHO + IPSS-R	WHO + WPSS
AIC	323.91	318.64	309.50	309.27	305.17	301.86
Relative AIC weights	0.000	0.000	0.018	0.02	0.154	0.808
Significant Cox models in bootstrap sets	100%	100%	100%	100%	84%	94%

Abbreviations: WHO, World Health Organisation; AIC, Akaike information criteria.

regressions were performed for each set under the same conditions as the calculations of the original data [2,6]. Finally, we compared the AIC values in the bootstrap sets by analysis of variance for repeated measures and the paired *t* test with correction of the alpha error by Cross and Chaffin [7].

Median observation time of the patients was 48 months. In May 2016, 52 patients were still alive. Patients had a median age of 64 years at diagnosis (range 15–93 years). According to the FAB classification, 56 cases were refractory anaemia, 17 were refractory anaemia with ring sideroblasts, 28 were refractory anaemia with excess of blasts and 4 refractory anaemia with excess of blasts in transformation. Cases of chronic myelomonocytic leukaemia were not included. According to the WHO 2008 criteria, there were 2 patients with 5q-syndrome, 7 with refractory cytopenias, 64 with refractory cytopenias with multilineage dysplasias and 28 with refractory anaemia with excess of blasts. Classifying according to the IPSS-R score, we found 14 very low risk, 40 low risk, 23 intermediate risk, 17 high risk, as well as, 7 very high risk patients. When applying the WPSS classification system, there were 3 patients with very low risk, 28 with low risk, 36 with intermediate risk, 22 with high risk and 6 with very high risk.

All four classifications discriminated significantly ($p < 0.05$) survival in univariate Cox regressions. This was also the case for the combinations WHO/IPSS-R and WHO/WPSS, but not for FAB/IPSS-R and FAB/WPSS combinations. In 100 bootstrap resampling sets, this was also true for the overwhelming majority of the cases (Table 1), whereas the combinations FAB/IPSS-R and FAB/WPSS yielded significant multivariate models in only 17% and 21% of the 100 sets, respectively and were therefore not considered in further evaluations.

AIC values of IPSS-R and WPSS were lower than those of the FAB and WHO classifications, and lowest for the combinations WHO/IPSS-R and WHO/WPSS, thus indicating that IPSS-R and WPSS explained better the survival curve than the FAB or WHO classification. The combinations WHO/IPSS-R and WHO/WPSS yielded the best prognostic information.

According to the original data, the models based on WPSS alone or in combination with the WHO classification seemed to be superior to those using IPSS-R. But this could be due to statistical fluctuations, since sometimes very few cases may be important for the model selection. To detect this effect, we compared the AIC values in the 100 bootstrap sets. Now the results of the original data set were confirmed in so far as the WHO classification had significant lower AICs than the FAB classification. Better values were found for IPSS-R and WPSS, but the best explanatory power was observed for the combinations WHO/IPSS-R and WHO/WPSS.

In the 100 resampling data sets, the AICs of IPSS-R scores were not significantly different from those of WPSS scores and in the same way, there were no significant differences between the AICs of the combined Cox regressions WHO/IPSS-R and WHO/WPSS, although this had been suggested by w values of the original data.

Thus our prospective study showed that IPSS-R and WPSS explain better the overall survival of MDS patients than the stratification according to the diagnostic classifications, thus confirming a part of the results of van Spronsen *et al* [1]. But our data also revealed that combined models containing the WHO 2008 classification yielded significantly better models than those based on a single classification. All these results were corroborated in a bootstrap resampling study, which underlines the stability of these models. We were, however, not able to show a relevant difference of the explanatory power between IPSS-R and WPSS, applied as a single variable or when combined with the WHO classification.

Therefore we conclude that, based on the Akaike information criteria, the WHO classification contains prognostically relevant information beyond IPSS-R or WPSS, at least regarding overall survival.

Conflict of interest statement

None declared.

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