The myelodysplastic syndrome-comorbidity index provides additional prognostic information on patients stratified according to the revised international prognostic scoring system

The myelodysplastic syndromes are a heterogeneous group of disorders of the hematopoietic stem cell and stem cell niche.[1] The revised version of the International Prognostic Scoring System (IPSS-R), which is based on disease-related factors, was recently published.[2] In 2010, the MDS-specific Comorbidity Index (MDS-CI) was developed by the Italian MDS study group and was validated using data of the Düsseldorf MDS-Registry. It uses patient-related factors.[3] We wondered if the MDS-CI adds any prognostic information to the IPSS-R. Our retrospective study included 1161 patients from the Düsseldorf MDS-Registry who received best supportive care or disease-specific therapy but not allogeneic transplantation. Diagnoses were made according to the WHO 2008 classification.[4] In addition, patients with chronic myelomonocytic leukemia (CMML)[5] and refractory anemia with excess blasts in transformation (RAEB-T)[6] were included. For each patient to be included in the study, a complete set of comorbidity factors had to be evaluable. Data of 504 patients of our cohort had been used as the validation cohort for the development of the MDS-CI. The study received local ethics committee approval.

Patients´ data are summarized in Table 1. According to the MDS-CI, median survival times were 39, 24 and 15 months, for the low-risk, intermediate-risk and high-risk groups, respectively (P<0.001). The most frequent comorbidities were cardiac diseases (37%), followed by solid tumors (10%), and pulmonary (9%), renal (7%) and hepatic diseases (4%). Male patients had more comorbidities than female patients (P=0.001). Cardiac and pulmonary diseases were more frequent in males than in females: 42% *vs.* 30% (P<0.001) and 11% *vs.* 6% (P=0.002), respectively. Survival of male patients in the whole cohort (P=0.002) and in the MDS-CI low-risk group was worse than survival of female patients (P=0.02). The IPSS-R assessed at diagnosis was available for 506 patients. Median survival times were 105, 70, 36, 14 and 8 months for the very low-risk, low-risk, intermediate-risk, high-risk and very high-risk groups, respectively; overall survival time was 37 months (P<0.001). The IPSS-R low-risk group was divided by the MDS-CI into three different risk groups with survival times of 92, 63 and 36 months, respectively (P<0.0001). Combining IPSS-R very low- and low-risk patients together (n=221) produced significantly different median survival times; 98, 70 and 45 months, respectively (P=0.005) (Figure 1). Patients assigned to the intermediate, high- and very high-risk groups were combined (n=285) and this produced significantly different median survival times; 22, 21 and 7 months, respectively (P=0.017) (Figure 1).

In the Cox regression model in categorical analysis, the five risk groups of the IPSS-R are included into the model, as well as the MDS-CI low- and intermediate-risk groups. In the forward stepwise multivariate Cox regression analysis, IPSS-R and MDS-CI provided independent prognostic information.

A total of 859 out of 1161 patients (74%) died during follow up. The exact cause of death could be ascertained in 516 patients. Of these, 402 deaths were disease-related (78%); in the other 114 patients, death was not disease-related (22%). Interestingly, in the MDS-CI low-risk group, the death of 84% of patients was disease-related: 75% of patients in the intermediate-risk group and 67% of those in the high-risk group (P=0.002).

Table 1. Patients' characteristics.

	N	n in %
Male	677	58
Female	484	42
Age >60 years	1003	86
Age >70 years	671	58
Age >80 years	206	18
HB in g/dL		
>10	471	41
8-10	394	34
<8	251	21
Missing	45	4
BM-Blast		
<3	429	37
3-4	229	20
5-10	235	20
>10	267	23
Missing	23	2
MDS-CI		
Low-risk group	583	50
Intermediate-risk group	419	36
High-risk group	159	14
IPSS-R		
Very low-risk group	64	13
Low-risk group	157	31
Intermediate-risk group	127	25
High-risk group	83	17
Very high-risk group	75	14

In a large cohort of 506 MDS patients, we were able to show that, in univariate analyses, the MDS-CI allows further stratification of the IPSS-R low-risk group and the combined group of the very low- plus low-risk groups and the intermediate- plus high-risk groups. In multivariate analyses, the MDS-CI provides prognostic stratification independently of the IPSS-R. We also showed that in the MDS-CI high-risk group, the proportion of patients who died from disease-related causes is smaller than in the MDS-CI low-risk group, underlining the importance of assessing and potentially treating comorbidities.

Our group was the first to systematically examine MDS patients according to comorbidities using CCI and HCTCI and evaluate the relationship to the IPSS.[7] We reported that the HCTCI is superior to CCI in the multivariate analysis including the IPSS. Since both scores were not optimally suited for MDS patients, the Italian study group developed the MDS-CI, which was validated using data from our Registry.[3] We can now confirm that the MDS-CI is suitable for all MDS patients. Breccia et al. compared the three mentioned comorbidity scores.[8] Sperr et al. used CCI and HCTCI, and in their cohort, the HCTCI further stratified the IPSS low- and IPSS intermediate-risk groups.[9] More recently, the Austrian MDS-Group published a score which is made up of both patient-related and disease-related factors with a comorbidity score according to HCTCI, ferritin, IPSS and age. The authors showed that this score provides four independent risk groups.[10]

In summary, a lot of work has been done to show that comorbidities are important for MDS-patient outcome. But do we really need another score? When you ask clinicians if they classify patients according to any comorbidity score they usually answer "No", except in patients for whom allogeneic transplantation is being programmed. We propose to use the MDS-CI for assessment of comorbidities in the future since it has shown its high stability in

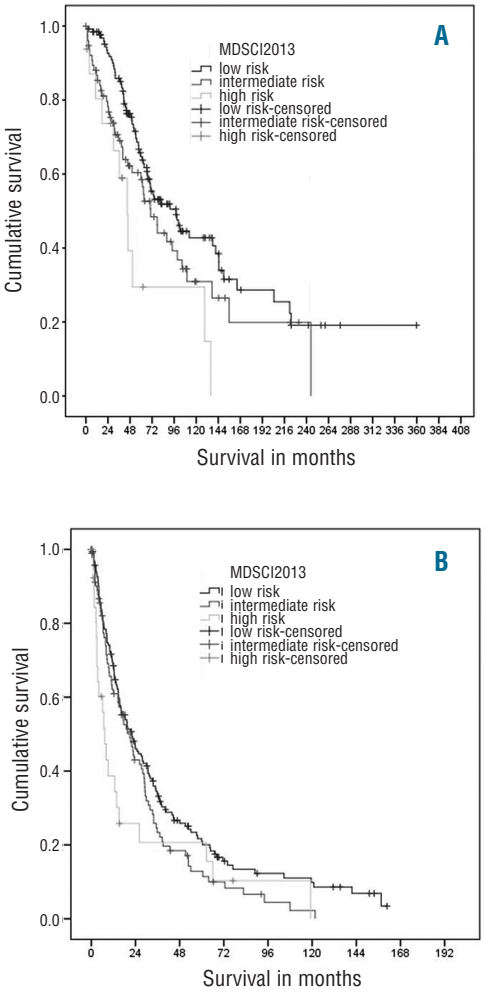

Figure 1. Kaplan-Meier curve of combined IPSS-R groups according to MDS-CI. (A). IPSS-R very low- plus low-risk group. (B). IPSS-R intermediate plus high- plus very high-risk group.

the hands of different study groups and has the most consistent results,[3,11] in contrast to the inconsistent results produced when using CCI and HCTCI to assess comorbidities for all MDS patients.[7,9,11,12] Furthermore, the MDS-CI is independent of the IPSS-R, as shown in our present study, and is independent of the WPSS, as shown by Breccia[8] and Della Porta[3] and co-workers. Comorbidities can be an important factor in clinical decision making. On the one hand, low-risk MDS patients with cardiac diseases should probably be treated for their cardiac disease since in these cases anemia worsens outcome. On the other hand, clinicians dare not give high-risk patients with comorbidities intensive therapy regimens. Undertreatment because of comorbidities has been reported, i.e. in breast cancer.[13] This is a call for a prospective assessment of comorbidities, particularly within clinical trials, to find out: i) if patients with one or more comorbidities profit from earlier therapy; ii) if it is reasonable to not treat patients with a high comorbidity score; and iii) to facilitate better comparisons of the MDS patient populations.

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