Comorbidity as prognostic variable in MDS: comparative evaluation of the HCT-CI and CCI in a core dataset of 419 patients of the Austrian MDS Study Group

W. R. Sperr1*, F. Wimazal1, M. Kundi2, C. Baumgartner1, T. Nösslinger3, A. Makrai3, R. Stauder4, O. Krieger5, M. Pfeilstöcker1,6 & P. Valent1,6

1Department of Internal Medicine I, Division of Hematology and Hemostaseology; 2Institute of Environmental Health, Medical University of Vienna, Vienna; 3Third Medical Department for Hematology and Oncology, Hanusch Hospital, Vienna; 4Department of Internal Medicine V, Haematology and Oncology, Medical University of Innsbruck, Innsbruck; 5Department of Internal Medicine I, Hospital of the Elisabethinen, Linz and 6Ludwig Boltzmann Cluster Oncology, Vienna, Austria

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Background: The evaluation of comorbidity is of increasing importance in patients with hematologic disorders.

Patients and methods: In the present study, the influence of comorbidity on survival and acute myeloid leukemia (AML) evolution was analyzed retrospectively in 419 patients with de novo myelodysplastic syndromes (MDS) (observation period: 1985–2007). The median age was 71 years (range 24–91 years). Two different scoring systems, the hematopoietic stem-cell transplantation-specific comorbidity index (HCT-CI) and the Charlson comorbidity index (CCI) were applied.

Results: The HCT-CI was found to be a significant prognostic factor for overall survival (OS, P < 0.05) as well as event-free survival (EFS, P < 0.05) in our patients, whereas the CCI was of prognostic significance for OS (P < 0.05), but not for EFS. For AML-free survival, neither the HCT-CI nor the CCI were of predictive value. A multivariate analysis including age, lactate dehydrogenase, ferritin, karyotype, number of cytopenias, French–American–British groups, and comorbidity was applied. Comorbidity was found to be an independent prognostic factor in patients with low- or int-1-risk MDS (P < 0.05) regarding OS and EFS.

Conclusions: Together, our data show that comorbidity is an important risk factor for OS and EFS in patients with MDS.

Key words: comorbidity, MDS, prognostication, survival

Introduction

Myelodysplastic syndromes (MDS) comprise a heterogeneous group of clonal hematologic malignancies characterized by a profound defect of myeloid stem cells resulting in bone marrow (BM) failure with dysplasia in one or more cell lineages and in the occurrence of cytopenia [1–5]. Traditionally, the classification of MDS is based on blast cell counts, signs of dysplasia, and karyotypes [6, 7]. Survival rates and transformation to secondary acute myeloid leukemia (AML) vary significantly among World Health Organization (WHO) or French–American–British (FAB) groups [8–10]. However, even within a particular WHO or FAB category, survival and AML transformation vary among patients [11]. Thus, it may be difficult to predict the clinical course for individual patients. To better predict survival and AML transformation in MDS, several prognostic scoring systems have been established in the past [12–20]. These scoring systems are based on multiple prognostically important parameters, including BM blasts, karyotype, and number of cytopenias. The gold standard for prognostication in MDS is the International Prognostic Scoring System (IPSS) [18]. Most scoring systems have been developed to better predict AML-free survival (AFS) in MDS, and therefore have included primarily disease-related factors [14–20].

Patient-related factors like chronic comorbid conditions, poor performance status, and abnormal organ function may also influence the outcome, especially the survival in patients with MDS [21]. This seems to be of particular importance as MDS is found primarily in elderly patients [22]. The prognostic value of comorbidity has recently been shown in patients who underwent allogeneic stem-cell transplantation as well as in elderly patients with AML [23–26]. So far, however, only little has been published on the impact of comorbidity in MDS [27].

The aim of this multicenter study was to evaluate the prognostic value of comorbidity in patients with de novo MDS.
To address this issue, two scoring systems, the Charlson comorbidity index (CCI) and the hematopoietic stem-cell transplantation-specific comorbidity index (HCT-CI), were applied and compared [23–26].

patients and methods

patients’ characteristics

A total number of 419 patients (in whom the IPSS was available) with primary (de novo) MDS seen in four hematologic centers of the Austrian MDS Study Group (Medical University of Vienna, Hansch Krankenhaus Vienna, Medical University of Innsbruck, Hospital of the Elisabethinen Linz, Austria) were analyzed retrospectively. The patients were diagnosed from 1985 to 2007. The median age was 71 years (range 24–91; 191 females and 228 males, female/male ratio 1 : 1.2). Detailed patients characteristics are shown in Table 1.

prognostic parameters

The following parameters were recorded at presentation: age, gender, cytogenetics (according to the IPSS), complete blood picture, differential count, lactate dehydrogenase (LDH) activity, FAB subtype, and ferritin. Karyotyping was carried out on unstimulated (24 h) BM cells according to standard techniques [28]. Karyotypes were classified and described according to the criteria provided by the International System for The Human Cytogenetic Nomenclature [29].

evaluation of comorbidity

Comorbidities were recorded at the time of diagnosis and analyzed retrospectively. Two previously published scoring systems, i.e. the CCI and the HCT-CI [23, 25], were applied. Both scoring systems take the presence or absence of several comorbid conditions and their severity into account.

statistical analysis

The product limit method of Kaplan and Meier was applied to analyze the probability of survival and AFS [30]. To calculate the significance of differences between risk groups, the log-rank test was applied. For analysis of overall survival (OS) and event-free survival (EFS), patients lost for follow-up or patients who received intensive chemotherapy, stem-cell transplantation, demethylating agents (azacitidine and decitabine), revlimid or amifostine were censored at the start of therapy. OS was defined as time from diagnosis to death. AFS was defined as time from diagnosis to AML evolution (blast cell count ≥50%). For analysis of AFS, patients who died before AML transformation were censored. EFS was calculated from diagnosis to AML evolution or death. Uni- and multivariate Cox regression analysis was carried out to evaluate the prognostic value of parameters (i.e. LDH and age) as well as the predictive potency of the different scoring systems (IPSS, CCI and HCT-CI). Differences were considered significant when the P value was <0.05.

results

follow-up and survival

Survival and AFS were analyzed in 419 patients. The median observation period was 1.2 years. Of the 419 patients, 179 died. The median OS of all patients included in our analyses was 3.3 years, and the median EPS was 2.49 years. The median AFS was not reached in the entire group. All in all, 19% of the patients developed secondary AML after a median time of 9.9 months (range 0.3–116.6 months). Significant differences in OS, EFS, and AFS were found among the IPSS risk groups (Table 2; P < 0.05).

comorbidities and comorbidity scoring systems

Cardiac disorders (i.e. infarction, coronary heart disease without infarction, cardiomyopathy, cardiac valve disease, or arrhythmia) were found to be the most frequent comorbidities in our patients. Other frequently observed comorbidities were peripheral or cerebral arterial occlusive disease and diabetes mellitus. Less frequent disorders found in our patients were neoplasms (for which patients had not received chemotherapy or radiation), gastrointestinal tract ulcer, chronic pulmonary disease, hepatic disorder, rheumatologic disease, psychiatric disturbance, renal dysfunction, infection, obesity, dementia, hemiplegia, and chronic inflammatory bowel disease, and one patient presented with a concomitant non-Hodgkin’s lymphoma (Table 3).

prognostic significance of comorbidity

As assessed by univariate analysis, the HCT-CI was found to be of prognostic significance for OS and EFS (P < 0.05; Figure 1).
The median OS in the low-risk group was 4.2 years, 3.2 years in the intermediate-risk group, and 2.2 years in the high-risk group. The EFS in the low-risk, intermediate-risk, and high-risk groups was 3.1, 2.5, and 1.5 years, respectively. The CCI was also of prognostic value for OS (median OS: no comorbidity risk points: 3.8 years; 1–2 points: 2.9 years; 3–4 points: 2.6 years; ≥5 points: not reached in seven patients) (P < 0.05). With regard to the EFS, however, the CCI was not of predictive value (P > 0.05). When calculating AFS, neither the CCI nor the HCT-CI were of prognostic significance (P > 0.05).

Analyzing the prognostic value of comorbidity in different IPSS risk groups, both the HCT-CI and the CCI were found to be significant prognostic factors for OS and EFS in patients with low-risk or int-1-risk MDS (Figure 2) (P < 0.05). Again, the comorbidity scores had no predictive value for AFS. In patients with int-2- or high-risk MDS, comorbidity was not found to be a prognostic marker.

**multivariate analysis**

To evaluate whether comorbid conditions are an independent prognostic parameter in patients with MDS, multivariate analyses were carried out. The following variables were included in these analyses together with the HCT-CT or the CCI: age, LDH levels, ferritin, FAB subgroup, number of cytopenias, and karyotype (according to the IPSS criteria).

Interestingly, analyzing the entire group of patients neither the HCT-CI nor the CCI were independent prognostic parameters for OS or EFS after addition of ferritin in the multivariate Cox model (Table 4). However, in patients with low- or int-1-risk MDS, chronic comorbid conditions were found to be an independent prognostic factor for OS and EFS even when adding ferritin levels in the Cox model (P < 0.05) (Table 4). In particular, the HCT-CI was a prognostic variable for OS (P < 0.05) and EFS (P < 0.05) in this group of patients independent of age, LDH, ferritin, FAB subgroup, number of cytopenias, and karyotype. In contrast, the CCI was not of prognostic

**Table 2.** Median survival (years) according to the IPSS

<table>
<thead>
<tr>
<th>IPSS</th>
<th>OS</th>
<th>AFS</th>
<th>EFS</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>6.65</td>
<td>n.r.</td>
<td>6.52</td>
<td>135</td>
</tr>
<tr>
<td>Int-1</td>
<td>2.83</td>
<td>9.71</td>
<td>2.28</td>
<td>158</td>
</tr>
<tr>
<td>Int-2</td>
<td>2.03</td>
<td>1.52</td>
<td>1.06</td>
<td>79</td>
</tr>
<tr>
<td>High</td>
<td>0.76</td>
<td>0.88</td>
<td>0.37</td>
<td>47</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

IPSS, International Prognostic Scoring System; OS, overall survival; AFS, AML-free survival; EFS, event-free survival; n.r., not reached yet.

**Table 3.** Frequencies of comorbidities

<table>
<thead>
<tr>
<th>Disorder</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disease</td>
<td>128</td>
</tr>
<tr>
<td></td>
<td>Infarction, n = 38; coronary heart disease without infarction, n = 23; cardiomyopathy, n = 15; cardiac valve disease, n = 12; arrhythmia, n = 40</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>CAOD, n = 28; PAOD, n = 22</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Without end organ damage, n = 35; with end organ damage; n = 12</td>
</tr>
<tr>
<td>Tumor</td>
<td>34</td>
</tr>
<tr>
<td>Gastrointestinal tract ulcer</td>
<td>26</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Mild, n = 16; severe, n = 1</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Mild, n = 9; severe, n = 5</td>
</tr>
<tr>
<td>Psychiatric disturbance</td>
<td>12</td>
</tr>
<tr>
<td>Rheumatologic disorders</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Connective tissue disease, n = 7; other, n = 2</td>
</tr>
<tr>
<td>Infection</td>
<td>8</td>
</tr>
<tr>
<td>Renal disease</td>
<td>7</td>
</tr>
<tr>
<td>Obesity</td>
<td>6</td>
</tr>
<tr>
<td>Dementia</td>
<td>6</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>3</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>2</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>1</td>
</tr>
</tbody>
</table>

Comorbidities were recorded at the time of diagnosis and analyzed retrospectively.

No chemotherapy or radiation was administered in these patients. CAOD, carotid artery occlusive disease; PAOD, peripheral arterial occlusive disease.

The median OS in the low-risk group was 4.2 years, 3.2 years in the intermediate-risk group, and 2.2 years in the high-risk group. The EFS in the low-risk, intermediate-risk, and high-risk groups was 3.1, 2.5, and 1.5 years, respectively. The CCI was also of prognostic value for OS (median OS: no comorbidity risk points: 3.8 years; 1–2 points: 2.9 years; 3–4 points: 2.6 years; ≥5 points: not reached in seven patients) (P < 0.05). With regard to the EFS, however, the CCI was not of predictive value (P > 0.05). When calculating AFS, neither the CCI nor the HCT-CI were of prognostic significance (P > 0.05).

Analyzing the prognostic value of comorbidity in different IPSS risk groups, both the HCT-CI and the CCI were found to be significant prognostic factors for OS and EFS in patients with low-risk or int-1-risk MDS (Figure 2) (P < 0.05). Again, the comorbidity scores had no predictive value for AFS. In patients with int-2- or high-risk MDS, comorbidity was not found to be a prognostic marker.
As well as AFS in our patients. However, within an IPSS risk group, the survival of patients varies markedly. Therefore, the inclusion of additional risk factors in scoring systems has been proposed [19, 31–33]. So far, disease-related factors like the LDH or the transfusion frequency have been proposed as additional prognostic variables in most studies [19, 33]. However, as patients with MDS comprise an elderly group with a median age of 70 years, patient-related factors like comorbid conditions may also be of interest as prognostic variables, especially for survival [21, 27, 34]. Indeed, in the present study, we were able to show that comorbidity is an important additional risk factor in MDS concerning survival.

The CCI is a commonly used scoring system to assess the prognostic risk of comorbid conditions. The CCI was originally developed to assess the 1-year mortality in patients with different diseases [25]. The CCI has also been applied to various types of cancer and leukemias, including patients with AML, breast cancer, colorectal cancer, oesophageal cancer, or non-Hodgkin’s lymphomas [23,35–40]. Therefore, this risk score was also applied in our patients. Moreover, an adapted version of this score published by Sorror et al. was used. This score was specifically adapted for patients with hematologic disorders and successfully applied in patients receiving a hematologic stem-cell transplant [23, 24, 26]. In our analysis, comorbid conditions defined by the HCT-CI and the CCI were found to be of prognostic value for the estimation of OS, and the HCT-CI was found to be also of prognostic significance for EFS estimation. In contrast, when calculating AFS, neither the CCI nor the HCT-CI were of predictive value.

As assessed by multivariate analysis including age, LDH levels, ferritin, FAB subgroup, number of cytopenias, as well as the karyotype (according to the IPSS criteria), neither the HCT-CI nor the CCI were independent prognostic parameters for OS or EFS. Interestingly, when adding LDH, FAB, cytopenias, or age, the HCT-CI and the CCI remained prognostically significant and independent variables, whereas serum ferritin levels were added, HCT-CI and CCI were no longer found to be independent prognostic variables. This observation suggests that elevated ferritin may be associated with organopathy and comorbidity in these patients. This association may be explained by the fact that various pathologic conditions such as chronic inflammation, vascular disorders, or neoplasms cause an increase in ferritin. Another (additional) explanation for the association between ferritin and comorbidity may be by a direct effect of iron overload on organ function (especially liver and heart), leading to organopathy and thus comorbidity. Another interesting observation was that in patients with low- or int-1-risk MDS, chronic comorbid conditions remained an independent prognostic factor for OS and EFS. This is in contrast to patients with int-2- or high-risk MDS patients, where comorbidity was no independent predictive factor for OS and EFS. However, it has to be pointed out that the group of patients with int-2- or high-risk MDS was relatively small.

All in all, assessment of comorbid conditions is of importance to estimate the probability of survival especially in patients with low- and int-1-risk MDS. In contrast, neither the HCT-CT nor the CCI were found to be significant prognostic factors for AML evolution. This may be of interest, since one could argue that some of the comorbidities may indeed also

![Graph](https://example.com/graph.png)

**Figure 2.** Overall survival (OS) and event-free survival (EFS) in patients with International Prognostic Scoring System (IPSS) low-risk and int-1-risk myelodysplastic syndrome. OS and EFS were calculated in IPSS low and int-1 patients \( (n = 293) \) by the method of Kaplan and Maier. The differences among the risk groups according to the hematopoietic stem-cell transplantation-specific comorbidity index (HCT-CI) were found to be significant \( (P < 0.05) \) when calculating the probability of OS (A) and EFS (B).

**Discussion**

In the present study, we have evaluated the prognostic value of two scoring systems for comorbid conditions, namely the HCT-CI and the CCI, in patients with de novo MDS. As assessed by univariate analysis, the HCT-CI was found to be a significant prognostic factor for OS and EFS \( (P < 0.05) \), and the CCI was of prognostic significance for OS. In multivariate analyses, comorbidity was found to be an independent prognostic factor in low- or int-1-risk MDS patients with regard to OS and EFS.

So far, the gold standard in prognostication of MDS is the IPSS [18]. Confirming previous studies [18], the IPSS was found to be an independent prognostic parameter for OS, EFS, as well as AFS in our patients. However, within an IPSS risk...
Table 4. Multivariate analysis of prognostic variables

<table>
<thead>
<tr>
<th></th>
<th>All patients, n = 419</th>
<th>Low or int-1, n = 293</th>
<th>Int-2 or high, n = 126</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OS HR</td>
<td>EFS P HR</td>
<td>OS HR</td>
</tr>
<tr>
<td>Agea</td>
<td>&lt;0.01 1.4 &lt;0.05 1.3 ns 1.2 ns 1.1</td>
<td>&lt;0.05 1.6</td>
<td>&lt;0.05 1.6</td>
</tr>
<tr>
<td>LDHb</td>
<td>ns 1.0</td>
<td>ns 1.0</td>
<td>ns 1.7 ns 2.2</td>
</tr>
<tr>
<td>Ferritin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.2 &lt;0.01 2.0</td>
<td>&lt;0.01 2.5 &lt;0.01 2.9</td>
<td>ns 1.8 ns 1.2</td>
</tr>
<tr>
<td>Karyotype</td>
<td>1.5 &lt;0.05 1.4</td>
<td>1.3 &lt;0.01 1.6</td>
<td>&lt;0.05 2.0 ns 1.3</td>
</tr>
<tr>
<td>Zytopenia</td>
<td>1.4 &lt;0.01 1.4</td>
<td>1.2 ns 1.2</td>
<td>ns 1.5 &lt;0.05 1.5</td>
</tr>
<tr>
<td>FAB</td>
<td>&lt;0.05 1.0 &lt;0.01 1.0</td>
<td>ns 1.0</td>
<td>ns 1.0</td>
</tr>
<tr>
<td>RA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.7 0.7</td>
<td>0.6 0.5</td>
<td>1.4 1.6</td>
</tr>
<tr>
<td>RARS</td>
<td>1.4 1.4</td>
<td>1.2 1.3</td>
<td>3.4 2.5</td>
</tr>
<tr>
<td>RAEB</td>
<td>2.1 3.5</td>
<td>4.1 8.4</td>
<td>4.5 6.1</td>
</tr>
<tr>
<td>RAEB-t</td>
<td>1.6 1.5</td>
<td>1.4 1.6</td>
<td>6.5 2.1</td>
</tr>
<tr>
<td>CMML</td>
<td>1.6 1.5</td>
<td>1.4 1.6</td>
<td>6.5 2.1</td>
</tr>
<tr>
<td>HCT-CI</td>
<td>ns 1.4</td>
<td>ns 1.2</td>
<td>&lt;0.05 1.4 &lt;0.01 1.6</td>
</tr>
</tbody>
</table>

<sup>a</sup>Decade.  
<sup>b</sup>Log scale.  
<sup>c</sup>Reference.

OS, overall survival; EFS, event-free survival; HR, hazard ratio; ns, not significant; LDH, lactate dehydrogenase; RA, refractory anemia; RARS, refractory anemia with excess of blasts; RAEB-t, refractory anemia with excess of blasts in transformation; CMML, chronic myelomonocytic leukemia.

Influence the evolution of the disease. Likewise, one can a priori not exclude an effect of certain comorbidities on leukemia development. For example, several of the comorbidities in elderly patients like diabetes mellitus or chronic infections may affect the immune system and thus immune surveillance and others like chronic autoimmunity reaction or vascular disorders may influence blast cell growth through cytokine effects. However, our data indicate that the progression of the disease depends on the biologic properties of the clone rather than on the comorbidity status of the patient. This is supported by the fact that the highest predictive value of comorbidity was observed in IPSS low- and int-1-risk patients, but was not observed in int-2- or high-risk MDS. On the other hand, the group of patients with int-2- and high-risk MDS was relatively small compared with patients with low and int-1 MDS. Here, studies including a larger sample size of int-2- and high-risk MDS patients will be required to further clarify this point in future studies.

Interestingly, the HCT-CI was found to differ from the CCI, especially in the multivariate analysis. This is of particular interest, since both scores reflect only the comorbid conditions. One explanation for the different prognostic impact of the scoring systems on survival could be that the HCT-CI was established specifically to predict the influence of comorbidity in patients with hematologic disorders, whereas the CCI is a general scoring system for comorbidity in various disease conditions. Thus, the HCT-CI might be a better predictor to detect the influence of comorbidity in patients with hematologic disorders. It may be of importance to assess comorbidity in patients eligible for stem-cell transplantation. Likewise, in case of a low comorbidity score but a high risk for AML evolution based on the IPSS, a patient would be an ideal candidate for transplantation.

Together, our data show that comorbidity is a significant prognostic risk factor for survival and EFS in patients with de novo MDS. Therefore, comorbidity should be considered as an important covariable in the risk assessment in MDS and in the overall treatment plan in these patients.

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