

Original Article

Verification of Survival Predictors in Elderly Patients with Myelodysplastic Syndrome from Outpatient Clinical Practice



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SUMMARY

Background: Myelodysplastic syndrome (MDS) is a clonal disorder affecting older persons. We aimed to analyze the effectiveness of the scoring systems and of the number of received red blood cell (RBC) units in predicting survival.

Methods: The study included an unselected group of 73 patients with MDS who were diagnosed and treated in a single hospital over a period of 12 years. International Prognostic Scoring System (IPSS), revised IPSS (IPSS-R), WHO-Prognostic Scoring System (WPSS), Charlson Age-Comorbidity Index (CACI), and impact of performance status (PS) on overall survival (OS) and event free survival (EFS) were tested. The follow-up of received RBC units was conducted.

Results: The median age at diagnosis was 69.5 years, the median CACI was 3.0. The median survival times of the group were 7.04 and 2.78 years for OS and EFS, respectively. The concordance values of the IPSS, IPSS-R and WPSS are 0.812, 0.892 and 0.889 for OS; 0.785, 0.847 and 0.827 for EFS. The comorbidity index and PS were the only auxiliary criteria when determining the risk and selecting the therapeutic approach in MDS patients. In transfusion-dependent unchelated patients, both OS and EFS were negatively influenced by both higher ferritin levels and the numbers of RBC units; however, the risk does not continue to increase after more than 20 RBC units are administered.

Conclusions: IPSS-R is best suited as a predictor of survival. CACI and PS present auxiliary criteria for determining the risk. Number of received RBC units was detected as a significant predictor of survival. Copyright © 2017, Taiwan Society of Geriatric Emergency & Critical Care Medicine. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Myelodysplastic syndrome is a heterogeneous group of hematopoietic disorders characterized by dysplastic changes in blood cell precursors in bone marrow, (pan) cytopenia in peripheral blood, and by various levels of risk for progression into acute leukemia¹. MDS develops either de novo or secondarily due to previous chemo- or radiotherapy. Diagnosis is based mainly on

microscopically detected significant dysplastic changes, an increased percentage of myeloblasts in a bone marrow smear, and identification of cytogenetic aberrations typical for MDS in patients with persistent or progressive cytopenia². Patient survival varies from several months to many years, depending on the MDS subtype, cytogenetic aberrations and depth of cytopenias³. Annual incidence in general population of developed countries is approximately five per 100,000, ranging from approximately 0.1 in patients aged under 40 years to more than 30 in those over 70 years of age and to approximately 50 per 100,000 in the 80+ age category. Thus, MDS represents a serious issue in geriatric hematology⁴.

The key to selecting the proper treatment modality is the classification of the patient into a risk group according to IPSS, IPSS-R or

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WPSS^{5–7}. Patient's age and comorbidities play an important role in selecting adequate therapy.

For many years, MDS management was mainly based on two modalities: supportive care including transfusions, and allogeneic stem cell transplantation. Novel drugs routinely used in clinical practice include hypomethylating agents, immunomodulators, or new chelating agents that may affect the natural course of the disease and prolong the survival of MDS patients⁸.

The objectives of the study were to provide a picture of the diagnosis and treatment of an unselected group of MDS patients cared for in the Zlín hospital in the setting of daily hematology practice over a long-term period (2002–2015) and to compare the results with the literature data. Frequently, data in literature is influenced by selection of certain patient groups (e.g. allogeneic transplantation, administration of hypomethylating agents), stemming from the fact that highly specialized hematology centers typically care for patients requiring curative or intensified therapy while those suitable for palliative therapy continue to be cared for in local hematology centers. Therefore, we aimed to determine which of the three prognostic indices is best for predicting OS and EFS. As MDS is mainly an old age disease usually accompanied by multiple comorbidities, we wanted to determine whether or not CACI⁹ is a stronger predictor of OS and EFS than the prognostic indices.

Transfusion of blood products remains the basis of MDS treatment even at the present time. Therefore, special attention is paid to the follow-up of the number of RBC units and serum ferritin levels in the subgroup with RBC transfusion-dependent patients.

2. Material and methods

Between January 1, 2002 and June 30, 2015, a total of 73 patients with MDS and chronic myelomonocytic leukemia (CMML) were diagnosed and treated in the outpatient center of the Hematology and Blood Transfusion Department of Tomáš Baťa Hospital in Zlín, often in collaboration with centers in Brno, Olomouc and Prague. The reason for including patients with CMML is a historical one since the older French-American-British (FAB) classification categorized the condition as belonging to the MDS groups of diseases¹. All patients came from the Zlín District with a population of approximately 200,000 inhabitants. Patient data has been kept in both the Zlín center and the MyDyS Registry 2.0 of the Czech MDS Group, a part of the Czech Medical Association of J. E. Purkyně.

Data selected for statistical analyses comprise sex, age at diagnosis, date of diagnosis and date of death or the last visit, 2008 WHO classification MDS subtype, risk groups according to the IPSS⁵, IPSS-R⁶ and WPSS⁷, presence/absence of cytogenetic aberrations, karyotype according to the IPSS and IPSS-R^{5,6}, presence/absence of bone marrow fibrosis in a bone marrow trephine biopsy sample, presence/absence of secondary MDS, date of progression, transfusion dependence according to the WPSS⁷, total RBC and platelet transfusions, performance status¹⁰, comorbidities expressed as the CACI⁹, treatment modalities used, and presence/absence of progression as of 30 June 2015¹¹. Diagnoses were made based on assessing peripheral blood smears, panoptic staining of sternal puncture samples (May-Grünwald, Giemsa-Romanowski)¹², sternal puncture samples stained to evaluate iron (Perls' reaction)¹³, classical karyotyping, and identification of cytogenetic aberrations typical for MDS in bone marrow using fluorescence in situ hybridization. For some patients, cytogenetic examination and trephine biopsy results are missing as they were not performed at all or valid samples were not obtained.

In 37 patients dependent on RBC transfusions, the follow-up was at 3, 6, 12 and 24 months and then at yearly intervals, starting from the onset of transfusion dependence. The parameters

followed were: ferritin and received RBC units. The data was related to those obtained at the time of diagnosis. Among the subjects, a small cohort of four patients was selected who underwent magnetic resonance imaging (MRI) of the heart using the T2* approach and MRI of the liver.

The patients mainly received outpatient treatment modalities, ranging from a watch and wait approach, transfusions with chelation, to erythropoiesis-stimulating protein (ESP) support, vitamins, immunosuppressants, low-dose chemotherapy (hydroxyurea, low-dose cytarabine), to immunomodulatory therapy with lenalidomide and administration of the hypomethylating agent 5-azacytidine (5-AZA), in cooperation with the centers in Brno, Olomouc and Prague.

Chelating agents were administered to low-risk transfusion-dependent patients with ferritin levels of at least 1000 µg/L. In the first years, only parenteral deferoxamine was used; later, patients included in a study carried out by the Czech MDS Group received deferiprone¹⁴; in the second part of the study period, deferasirox was administered. To reduce or completely eliminate their dependence on transfusions, low-risk patients received ESPs, either alone or in combination with granulocyte colony-stimulating factor. Immunosuppressive therapy with prednisone and/or cyclosporine A was instituted in patients with hypoplastic MDS confirmed by trephine biopsy. Combination chemotherapy (7 + 3) and allogeneic stem cell transplantations were carried out in the referral university hospitals.

All participants signed an informed consent form. This study was approved by the medical ethics committee of the Tomáš Baťa Hospital in Zlín, Czech Republic.

2.1. Statistical methods

Overall survival is defined as the time from diagnosis to death from any cause (event) or the last visit (censoring). Event-free survival is defined as the time from diagnosis to disease progression (a higher degree of cytopenia, higher number of blasts in the bone marrow, progression in the FAB classification) or death from any cause (event) or the last visit (censoring)¹¹. The impact of individual prognostic factors on OS and EFS was assessed by the Cox proportional hazard model. Concordance was used to determine the predictive power of the prognostic indices IPSS, WPSS and IPSS-R. Concordance measures the probability of agreement between survival times in a randomly selected pair of patients and their scores. Agreement means that a patient with a shorter survival time also has a less favorable score. Concordance always ranges from 0.5 (if the score has no predictive value for survival) to 1.0 (if all patient pair scores agree with their survival times). The relationship between two categorical predictors (e.g. the presence of secondary MDS and a prognostic index) was analyzed using contingency tables and a test of independence. The analyses were mostly performed with the Statistica software package; the Cox regression model was implemented in the R software. Effects with p-values below 0.05 were considered statistically significant.

3. Results and discussion

3.1. Sample characteristics

Of the 73 patients, 50 cases (68.5%) had low-risk MDS, comprising refractory anemia (RA), refractory cytopenia with unilineage dysplasia (RCUD), refractory anemia with ring sideroblasts (RARS), refractory cytopenia with multilineage dysplasia (RCMD), unidentified MDS (MDS-U), and MDS with isolated deletion 5q. Another 17 patients (23.3%) were in the high-risk MDS group, that is, subtypes of refractory anemia with excess blasts I and II (RAEB I

and II). The remaining six patients (8.2%) were diagnosed with CMML. In the entire sample, there was a slight preponderance of females (39 patients, 53%). The median age at diagnosis was 69.5 years (range, 38–87 years). Thirteen patients (18%) had secondary MDS or CMML. Cytogenetic aberrations were noted in 28 (42%) out of 66 evaluable patients. Bone marrow fibrosis was present in five of 54 patients who had a valid trephine biopsy sample at the time of diagnosis. Stratification of patients according to the IPSS, IPSS-R and WPSS is shown in Fig. 1. Further, 37 out of all 73 patients were dependent on RBC transfusions, seven of them received chelation therapy (Table 1). All treatment modalities and their combinations are summarized in Fig. 2.

3.2. Predictors of survival

The median survival times of all 73 patients were 7.04 and 2.78 years for OS and EFS, respectively. We first investigated the predictive power of the IPSS, WPSS and IPSS-R in the unselected cohort of patients. Both concordance of the three indices (see 2.1) and their ability to find statistically significant differences between prognostic groups were assessed. The Cox proportional hazard model was used to create a model in which the only predictor of survival (OS or EFS) is the patient's category according to the IPSS, WPSS or IPSS-R. Patients with IPSS (IPSS-R, WPSS) equal to 0 are always considered as the reference group. For OS, the concordance rates of the IPSS, IPSS-R and WPSS were 0.812, 0.892 and 0.889, suggesting that the WPSS is as good a predictor of OS as the IPSS-R. However, there were no statistically significant differences between the first three WPSS categories (i.e. very low, low and intermediate risk). Thus, the best predictor of OS in our patients continued to be, as expected, the IPSS-R, with statistically significant differences between all categories and a reasonable stratification of risk among the categories. It must be stressed that the IPSS has one category less than the IPSS-R, meaning that even if both indices were equally suitable, the IPSS concordance value should be higher. Therefore, the lower concordance value of the IPSS shows that the IPSS-R is a considerably better predictor of OS in this cohort. Similarly, the IPSS-R is the best prognostic index for EFS.

In the present study, valid cytogenetic data for several patients are missing. Those patients could not be classified into prognostic categories according to the IPSS, IPSS-R or WPSS. That is why we decided to verify whether the MDS subtype alone is an effective predictor of OS and EFS. For the purposes of analytical statistics, the 2008 WHO MDS subtypes were first divided into three diagnostic categories as follows: low-risk MDS comprising RA, RCMD, RCUd and MDS with isolated deletion 5q; high-risk MDS including RAEB I

Table 1
Transfusion-dependent patients receiving chelation therapy.

Patient	IPSS-R	RBC units	Chelating agents	Other treatments
1	Very low	110	DES; FER; EXJ	VIT; ESP + G-CSF
2	High	188	EXJ	5-AZA
3	Low	107	EXJ	VIT; ESP; 5-AZA
4	Low	244	FER; EXJ	VIT; ESP; PRED; LEN cons.
5	NA	56	DES	VIT; PRED; cyclosporine A
6	Low	86	EXJ	VIT
7	Very low	226	FER, DES, EXJ	VIT; LEN cons.; 5-AZA cons.

Cons.: considered; DES: deferoxamine; ESP: erythropoiesis-stimulating protein; EXJ: deferasirox; FER: deferiprone; G-CSF: granulocyte colony-stimulating factor; IPSS-R: Revised International Prognostic Scoring System; LEN: lenalidomide; NA: not available; PRED: prednisone; RBC: red blood cell; VIT: vitamins; 5-AZA: 5-azacytidine.

and II; and CMML, including CMML I and II. Once again, the category was the only predictor in the Cox proportional hazard model. In case of OS, HR = 7.4 for high-risk MDS vs. low-risk MDS, while HR = 11.9 for CMML vs. low-risk MDS. As for EFS, HR = 8.2 for high-risk MDS vs. low-risk MDS, while HR = 13.2 for CMML vs. low-risk MDS. In all four cases, the differences were statistically significant. Thus, the WHO subtype is a relatively good predictor of patient survival if valid cytogenetic data are not available.

In the present study, the median and mean ages of MDS patients at diagnosis were 69.5 and 67.5 years, respectively, which is consistent with literature data^{4,15}. People aged older than 65 years normally have three or more comorbid conditions; the same is true for MDS patients. Comorbidities generally adversely affect survival of patients with malignancies, and considerably influence therapeutic goals^{16,17}. Yet comorbidity scores are not included in the IPSS, IPSS-R or WPSS. In the present study, the median and mean CACI scores were 3.0 and 3.74, respectively. Statistical analysis showed that the CACI score was a significant predictor of both OS (a hazard ratio of 1.22 in patients having a difference of 1 between their CACI scores, p = 0.02) and EFS (HR = 1.20, p = 0.02). Classification of the CACI scores into five categories to match with the IPSS-R showed that this predictor has less power than the IPSS-R for both OS and EFS. Similarly, the statistical analysis failed to show that the PS score is better at predicting OS and EFS than any of the three prognostic indices.

Despite all the advances in pharmacological therapy of MDS, such as the use of lenalidomide or hypomethylating agents, supportive care including transfusion of blood products remains the cornerstone of treatment¹⁸. Repeated RBC transfusions, however, are associated with iron overload. The amount of iron in the body may be determined by both direct and indirect methods. The

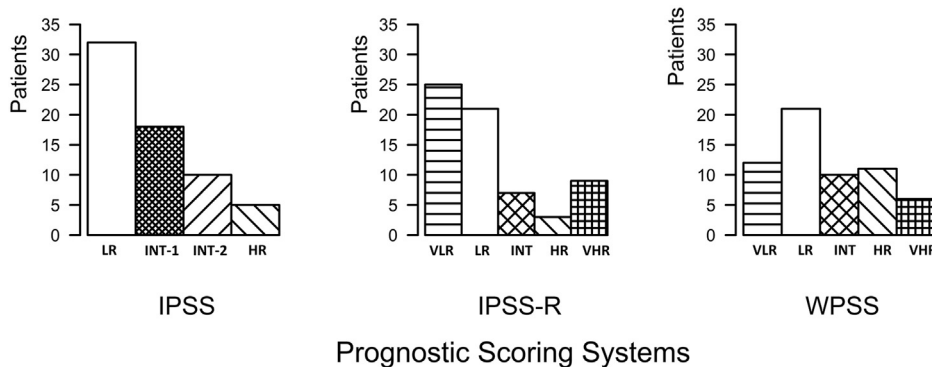


Fig. 1. Stratification of patients by the risk of progression to acute myeloid leukemia. HR: high risk; INT: intermediate risk; INT-1: intermediate-1 risk; INT-2: intermediate-2 risk; IPSS: International Prognostic Scoring System; IPSS-R: Revised International Prognostic Scoring System; LR: low risk; VHR: very high risk; VLR: very low risk; WPSS: World Health Organization Prognostic Scoring System.

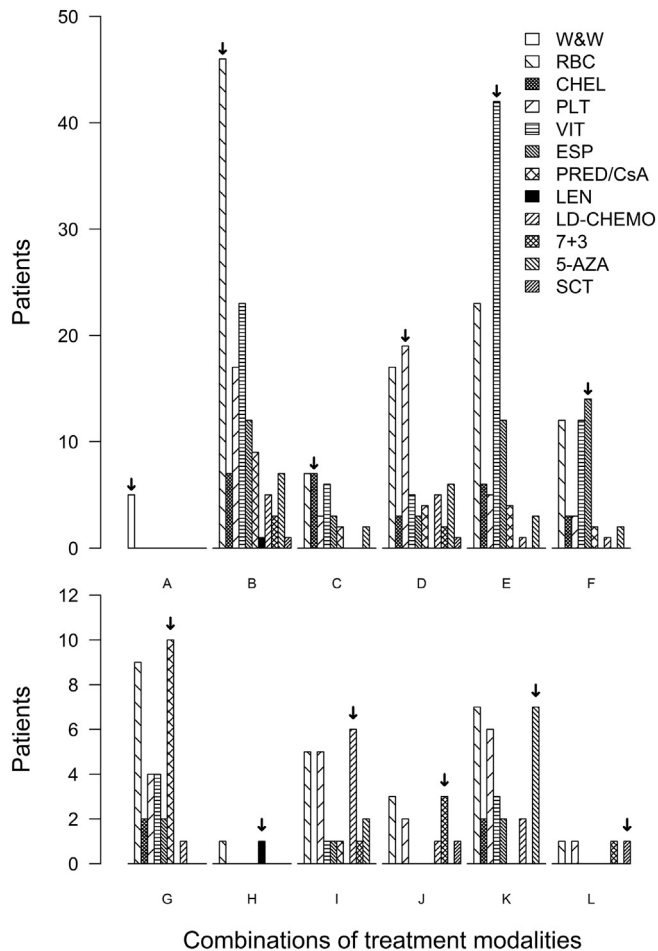


Fig. 2. Overview of treatment modalities. A–L: combinations of treatment modalities. The arrows show the total number of patients that received the particular therapy. ESP: erythropoiesis-stimulating proteins (darbepoietin alfa or recombinant human erythropoietin-rHuEPO); CHEL: chelation therapy (deferoxamine and/or deferiprone and/or deferasirox); LD-CHEMO: hydroxyurea or low-dose cytarabine; LEN: lenalidomide; PLT: platelet transfusion; PRED/CsA: prednisone and/or cyclosporine A; RBC: red blood cell transfusion; SCT: stem cell transplantation; VIT: vitamins and antioxidants (B-group vitamins, folic acid and antioxidants in the form of N-acetylcysteine and flavonoid-rich foods); W&W: watch and wait; 5-AZA: 5-azacytidine; 7 + 3: combination chemotherapy (cytarabine + daunorubicin or idarubicin).

simplest, most available and least expensive approach is the measurement of serum ferritin levels. However, these are only loosely correlated with the degree of iron overload as they are influenced by other factors, such as inflammation, liver damage or neoplasms¹⁹. This is well evidenced by the correlation between ferritin levels and numbers of RBC units received by unchelated patients in the present study. Although the correlation of both variables is positive ($r = 0.22$), it is very small and statistically insignificant. However, ferritin levels were shown to negatively influence both OS and EFS. In the case of OS, the hazard ratio was 1.2 ($p < 0.001$) in groups having a difference of 100 units between their ferritin levels; in the case of EFS, the HR was 1.14 ($p = 0.001$).

The indirect method used in the study for measuring iron overload was MRI of the liver and the myocardium using the T2* R2* approach, allowing semiquantitative assessment of both iron content in the myocardium, and of ventricular function¹⁹. Thus, the small cohort of four patients was selected among subjects in the present study. Observations of individuals suggest that iron overload of organs may occur with serum ferritin levels as low as approximately 500 $\mu\text{g/L}$ (Table 2).

Table 2
Patients undergoing MRI of the liver and heart.

Patient	HIO	CIO	Ferritin	HH	IPSS-R	RBC units	Chelation
1	Yes	No	1342	No	Very low	110	Yes
2	Yes	No	450	No	Low	45	No
3	Yes	No	1116	No	High	188	Yes
4	Yes	No	502	Yes	Very low	0	No

CIO: cardiac iron overload; FERRITIN: ferritin level [$\mu\text{g/L}$]; HH: hemochromatosis S65C heterozygosity; HIO: hepatic iron overload; IPSS-R: Revised International Prognostic Scoring System; RBC: red blood cell.

Iron chelation therapy has been included in all recommendations for treatment of MDS patients in the developed world. There is no consistent answer to the question of when chelation should be initiated. For example, the US National Comprehensive Cancer Network recommends to start chelation when ferritin concentration exceeds 2500 $\mu\text{g/L}$ ²⁰. According to the Czech guidelines, chelation therapy should be initiated in MDS patients with serum ferritin levels over 1000 $\mu\text{g/L}$ (after administration of approximately 20–25 RBC units), expected to have long-term transfusion dependence and having stable disease without survival-limiting comorbidities⁴. In the light of these facts, the findings concerning the relationship between OS and number of RBC units administered to unchelated patients identified in the present study are of interest. For that purpose, RBC units were classified into four groups as follows: 0, 1–10, 11–20, >20. Compared with baseline (0), the 1–10 group has a significantly higher risk of death ($\text{HR} = 8.4$, $p = 0.01$); this is even higher in the case of the 11–20 group ($\text{HR} = 22$, $p < 0.001$). Interestingly, the risk does not continue to increase after administering more than 20 RBC units. For EFS, the results were very similar ($\text{HR} = 9.1$, $p = 0.001$ for the 1–10 group; $\text{HR} = 20$, $p < 0.001$ for the 11–20 group).

4. Conclusion

The study showed that even for the unselected sample of MDS and CMML patients, any of the three prognostic indices may serve as a sufficiently effective predictor of survival, with the IPSS-R being the best predictor of both OS and EFS. In cases when valid cytogenetic findings are unavailable and patients therefore cannot be classified into prognostic groups, MDS subtypes according to the 2008 WHO classification remain a relatively good predictor of survival. The comorbidity index and PS were found to be only auxiliary criteria when determining the risk and selecting the therapeutic approach in MDS patients. In transfusion-dependent unchelated patients, both OS and EFS were negatively influenced by both higher ferritin levels and the numbers of RBC units; however, the risk does not continue to increase after more than 20 RBC units are administered.

Conflicts of interest

We have no financial or nonfinancial interests related to the material in the manuscript.

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Abbreviations

5-AZA 5-azacytidine
ESP erythropoiesis-stimulating protein

EFS	event-free survival
FAB	French-American-British
G-CSF	granulocyte colony-stimulating factor
HR	hazard ratio
CACI	Charlson Age-Comorbidity Index
CMML	chronic myelomonocytic leukemia
IPSS	International Prognostic Scoring System
IPSS-R	Revised International Prognostic Scoring System
MRI	magnetic resonance imaging
MDS	myelodysplastic syndrome
MDS/MPS	myelodysplastic/myeloproliferative neoplasms
OS	overall survival
PS	performance status
RBC	red blood cell
RA	refractory anemia
RAEB	refractory anemia with excess blasts
RARS	refractory anemia with ring sideroblasts
RCMD	refractory cytopenia with multilineage dysplasia
RCUD	refractory cytopenia with unilineage dysplasia
WHO	World Health Organization
WPSS	World Health Organization Prognostic Scoring System

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