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A model for the functional assessment of elderly with myeloid neoplasms



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ABSTRACT

Objective: Myeloid neoplasms are heterogeneous diseases that are more incident in the elderly. The goals of this study were to aggregate a geriatric approach to the patient assessment, to show the impact of gender, age, hemoglobin concentration and comorbidities on the functionality of elderly with myeloid neoplasms and to better understand how the instruments of functional assessment work according to the aggressiveness of the disease. **Methods:** Elderly patients (≥ 60 years old) with myeloid neoplasms were assessed using the Karnofsky scale, Eastern Cooperative Oncologic Group scale, and basic and instrumental activities of daily living scales. The hematopoietic cell transplantation-comorbidity index assessed the comorbidities. A mixed logistical regression model was fitted to estimate the impact of gender, age, hemoglobin concentration and the hematopoietic cell transplantation-comorbidity index on patients' functionality.

Results: Eighty-two patients with a mean age of 72.8 years (range: 60–92 years) were evaluated. Eighty percent had good Karnofsky and Eastern Cooperative Oncologic Group scales and 39% were independent according to the daily living activity scales. All of the patients with poor Karnofsky and Eastern Cooperative Oncologic Group scales were classified as dependent by the daily living activity scales. The mixed logistic regression models showed that age, gender, hemoglobin concentration and the comorbidity index impacted on the daily living activity scales. Karnofsky and Eastern Cooperative Oncologic Group scales were affected by hemoglobin and the comorbidity index. The model hypothesized the hemoglobin concentration at which there was a higher risk of poor Karnofsky and Eastern Cooperative Oncologic Group scales. This hemoglobin concentration depended on comorbidities and on the aggressiveness of the myeloid neoplasm.

Conclusion: The geriatric approach improved the sensitivity and specificity of the patients' assessment. Hemoglobin concentration associated to the risk of poor Karnofsky and Eastern Cooperative Oncologic Group scales depended on the comorbidity score and on the disease aggressiveness. The Karnofsky and Eastern Cooperative Oncologic Group scales had higher sensitivity in patients with more aggressive diseases.

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Introduction

Myeloid neoplasms (MN) are a group of heterogeneous diseases that include myeloproliferative neoplasms (MPN), myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). All these diagnosis are more incident and prevalent in elderly individuals.

This group of diseases includes from indolent entities such as polycythemia vera and essential thrombocythemia, to aggressive diseases, such as AML and MDS with excess of blasts. Chronic myeloid leukemia and myelofibrosis have some risk to evolve aggressively.¹

The management of older individuals with MN takes into account characteristics related to the patient and to the disease.²⁻⁶ The chronological age, the performance status (PS) and the comorbidity score are patient-related variables that are considered during treatment decision making of elderly individuals.⁷⁻⁹

The PS assessment is carried out using the Karnofsky Performance Scale¹⁰ (KPS) or by the Eastern Cooperative Oncologic Group¹¹ (ECOG) scale. However, over the last thirty years, several studies have demonstrated the low sensitivity of these instruments to evaluate function in older individuals with cancer.¹²⁻¹⁴ Thus, it has been recommended to aggregate geriatric tools to the PS assessment.

The major clinical challenge in the management of all myeloid neoplasms is the treatment of AML in older patients. Depending on the clinical and functional reserve of the patient, the therapeutic approach may be excessively toxic.² Thus, it is very helpful to distinguish the impact of the aging process separated from the impact of the disease.¹⁵

The objectives of this study were to assess the functionality of elderly patients with MN aggregating the basic activity¹⁶ (ADL) and instrumental activity¹⁷ (IADL) of daily living scales to the KPS and ECOG and to evaluate the impact of gender, age, hemoglobin (Hb) concentration and comorbidity score on the functionality of these patients. A third objective was to design a model to show how functional assessment instruments work in respect to the aggressiveness of the disease.

Methods

Elderly patients (≥ 60 years old) with MN followed at the Hematologic Outpatient Clinic of the Universidade Federal de São Paulo, (UNIFESP) were included in this study.

Diagnoses were based on the World Health Organization (WHO) Classification of tumors of hematopoietic and lymphoid tissues¹⁸ using the analysis of peripheral blood and bone marrow smears, the histology of bone marrow biopsy, and immunophenotypic, cytogenetic and molecular studies.

The patient's functional evaluation was performed by a hematologist just before the clinical consultation and included PS assessed employing the KPS and ECOG scales and functional status with the ADL and IADL scales. Comorbidities were evaluated according to the hematopoietic cell transplantation-comorbidity index (HCT-CI) developed by Sorror in 2005.¹⁹

The Hb concentration was measured by an automated technique employing a multichannel hematology analyzer (CELL-DYN Ruby, Abbott Diagnostic Division) using a blood sample taken before the consultation.

Patients with transfusion positive status received red blood cells prior to the determination of the Hb concentration in the month preceding the functional assessment. The decision to transfuse was based on the drop in Hb and its related symptoms. Demographic and clinical data were obtained from medical records.

The study was approved by Research Ethics Committee of UNIFESP (#0262/10) and the procedures undertaken were in accordance with the Declaration of Helsinki of 1975, revised in 2008.²⁰ All patients signed informed consent forms.

Statistical analysis

Analyses of means of age and Hb concentration were performed using Student's t test or ANOVA with Tukey's test. The frequencies of categorical variables were evaluated with Fisher's exact test.

Two mixed logistic regression models were fitted to assess the impact of gender, age, HCT-CI and Hb concentration on PS, dichotomized as good (KPS $\geq 80\%$ and ECOG < 2) or poor, and on functional status, as independent or dependent (need help in at least one daily task).

Generally, mixed models consider the information hierarchically structured at the unit and cluster levels. These cluster levels result from a grouping process outlined by characteristics shared by the units. Moreover, in mixed models the assumption of independence is violated, because there is a correlation between the units that belong to the same cluster. Random effects are included on considering this fact.

Mixed models incorporate these random effects and estimate them for each group. Therefore, the groups are represented by random effects and the variability across the groups is described by the intercept or the slope variability. The mixed model belongs to generalized linear mixed models (MLGM), which is an extension of generalized linear models (GLM).^{21,22}

Statistical analysis was performed using R statistics (v2.15) and the Statistical Package for the Social Sciences (SPSS – v18).

Results

Eighty-two patients, 40 men and 42 women, with a mean age of 72.8 years old (range: 60–92 years), were evaluated. Table 1 shows the descriptive statistics of the demographic data, functionality scores and comorbidity indices.

Of the fifteen patients with polycythemia vera (PV) and six with essential thrombocythemia (ET), 73% and 50% were JAKV617F positive, respectively. Ninety percent of these patients were taking hydroxycarbamide to control the disease.

All the nine patients who had chronic myeloid leukemia (CML) were in the chronic phase; seven were taking imatinib mesylate and four were in molecular remission.

Nine out of 25 patients with myelofibrosis (MF) were in the sclerotic phase, two in blastic transformation and the remaining 14 were in the cellular phase. Eleven patients were JAKV617F positive and 80% were taking hydroxycarbamide.

Table 1 – Age, gender, functionality scores and comorbidity indices stratified by myeloid neoplasm.

MN (n)	Age (years) ^a	Gender (n = male)	KPS ^b	ECOG ^b	ADL ^b	IADL ^b	HCT-CI (n)		
							Index 0	Index 1-2	Index ≥ 3
PV (15)	70.8 (60-83; 7.5)	10	100 (70-100)	0 (0-1)	6 (5-6)	27 (11-27)	6	5	4
ET (6)	72.3 (63-83; 8.2)	1	85 (60-100)	0.5 (0-2)	5.5 (5-6)	26.5 (18-27)	1	3	2
CML (9)	74.9 (63-88; 7.6)	3	90 (60-100)	0 (0-1)	6 (6-6)	26 (14-27)	6	3	0
MF (25)	72.7 (61-92; 8.5)	14	90 (40-100)	1 (0-2)	6 (4-6)	27 (11-27)	15	2	8
MDS (17)	74.4 (64-90; 8.2)	6	90 (40-100)	1 (0-3)	6 (3-6)	25 (12-27)	5	7	5
AML (10)	71.9 (61-84; 7.5)	6	70 (30-100)	2 (0-3)	5.5 (1-6)	16.5 (9-27)	5	4	1
TOTAL (82)	72.8 (60-92; 7.9)	40	90 (30-100)	0 (0-3)	6 (1-6)	26 (9-27)	38	24	20

MN: myeloid neoplasm; PV: polycythemia vera; ET: essential thrombocythemia; CML: chronic myeloid leukemia; MF: myelofibrosis; MDS: myelodysplastic syndromes; AML: acute myeloid leukemia; KPS: Karnofsky performance scale; ECOG: Eastern Cooperative Oncology Group scale; ADL: basic activities of daily living scale; IADL: instrumental activities of daily living scale; HCT-CI: hematopoietic cell transplantation-comorbidity index.

^a Mean (min-max; standard deviation).

^b Median.

Two out of 17 patients with MDS had refractory anemia with excess blasts (RAEB), one had refractory anemia (RA), four had refractory anemia with ringed sideroblasts (RARS), two had isolated del(5q) and six had refractory cytopenia with multilineage dysplasia (RCMD). Two MDS patients were treated with hypomethylating more than six months prior to the functional evaluation. In addition, two patients were on the thalidomide protocol²³ and two had received this drug more than six months prior to the functional assessment. Two patients with chronic myelomonocytic leukemia were included in the MDS group.

Six out of ten patients with AML had received chemotherapy, on average, 86 days before the evaluation and were in hematological remission at the moment of the functional assessment. There were seven AML not otherwise specified, two with myelodysplasia-related changes and one with recurrent genetic abnormalities [t(8;21)].

The Hb concentration, the incidence of anemia and the transfusion status were different across the MN types (Table 2). In view of this evidence, patients were divided into: Group I (PV, ET and CML), II (MF) and III (MDS and AML).

The Hb concentration was higher in patients with good PS (KPS/ECOG) than in patients with poor PS (p -value < 0.01). Likewise, the Hb concentration was higher in independent patients (ADL/IADL) than in those with dependence in daily tasks (p -value < 0.01). Patients with some dependence in daily activities were older than those with no dependence in ADL/IADL (p -value < 0.01). There was no significant difference in age between patients with good and poor PS. Women had higher ADL/IADL dependence scores than men (p -value < 0.01).

Eighty percent ($n = 65$) of the patients had good PS, however 50% of these patients ($n = 33$) had some dependence in daily activities. Seventeen patients had poor PS and all of them were dependent for some daily activities (Table 3).

There were patients with good PS and independent; others with good PS and dependent and, finally, there were patients with poor PS, all of who had some dependence for daily tasks (Table 4).

Table 4 shows that when compared to Groups I and II, Group III (MDS and AML) had a higher number of patients with poor PS and lower number of patients with good PS but dependent.

Table 2 – Grouping of patients based on mean Hb concentration and transfusion demand.

		Group I			Group II	Group III		p-value
		PV (n = 15)	ET (n = 6)	CML (n = 9)	MF (n = 25)	MDS (n = 17)	AML (n = 10)	
Hb (g/dL)		14.8 ^a (12.1-16.8; 1.51)	13.55 ^a (11.8-15.1; 1.31)	12.13 (11.0-13.2; 0.78)	11.33 ^a (3.5-15.1; 2.90)	9.99 ^a (6.3-12.9; 1.54)	9.66 ^a (5.9-13.0; 2.36)	<0.01 ^a
Tx	Yes	0	0	0	7	7	8	<0.001 ^b
	No	15	6	9	18	10	2	

PV: polycythemia vera; ET: essential thrombocythemia; CML: chronic myeloid leukemia; MF: myelofibrosis; MDS: myelodysplastic syndromes; AML: acute myeloid leukemia; Hb: hemoglobin concentration; TX: red cell transfusion during 30 days before functional assessment.

^a Identify significant differences (ANOVA with Tukey's test).

^b Fisher's test.

Table 3 – Distribution of patients by performance and functional status.

Functional status	Performance status		Total
	Good	Poor	
Independent	32 (50%)	0	32
Dependent	33 (50%)	17 (100%)	50
Total	65	17	82

Good performance status: KPS $\geq$ 80% and ECOG $<$ 2; Independent: no dependence for ADL and IADL.

Table 4 – Distribution of patients by groups and functionality.

Groups (n)	Good performance status		Poor performance status
	Independent	Dependent	Dependent
I – PV + ET + CML (30)	13	14	3
II – MF (25)	13	11	1
III – MDS + AML (27)	6	8	13
TOTAL (82)	^a p = 0.001		

Good performance Status: KPS $\geq$ 80% and ECOG $<$ 2; Independent: no dependence in ADL and IADL.
 PV: polycythemia vera; ET: essential thrombocythemia; CML: chronic myeloid leukemia; MF: myelofibrosis; MDS: myelodysplastic syndrome; AML: acute myeloid leukemia.
^a Fisher's exact test.

A mixed logistic regression model was applied to explain PS (by KPS and ECOG scales) which was influenced by Hb concentration (p -value = 0.019) and HCT-CI (p -value = 0.07). Gender (p -value = 0.22) and age (p -value = 0.77) did not impact on the PS. Thus, the final logistic model included only the Hb concentration and HCT-CI. The variance of the random effect of grouping was 1.18. The random effects (intercepts) in Groups I, II, and III were 0.27, -1.15 and 1.06, respectively.

The hypothetical Hb concentrations at which there were increased risks of having poor PS are reported in Table 5. These Hb concentrations depended on the group (I, II or III) and on the HCT-CI (0, 1, 2 or $\geq$ 3). This model had an area under the receiver operating characteristic (ROC) curve of 0.85, with sensitivity of 76% and specificity of 75%.

A mixed logistic regression also demonstrated the impact of age (p -value = 0.006), gender (p -value = 0.002), comorbidities

(p -value = 0.014) and Hb concentration (p -value = 0.058) on the functional status (by ADL and IADL). The variance of random effect of grouping was 0.09. The random effects (intercepts) in Groups I, II, and III were 0.07, -0.23 and 0.16, respectively.

Considering similar conditions of comorbidities, Hb and age, female patients were more likely to be dependent in some daily activity than the male individuals. Older age and higher HCT-CI and lower Hb concentration increased the likelihood of functional dependence. This model indicated a value of 0.84 for the area under the ROC curve, with sensitivity of 74% and specificity of 72%, indicating good predictive power.

Discussion

This study showed that the sensitivity of the functional assessment of these elderly patients with MN was increased by adding ADL and IADL to the KPS/ECOG. This was proven by the fact that 50% of the patients with good PS had some dependence in daily activities (Table 3).

On the other hand, the heterogeneity of MN showed that KPS and ECOG had different sensitivity and specificity depending on the clinical context they were applied in. In this study, these instruments had higher sensitivity and specificity in patients with AML and MDS. As illustrated by Table 4, this group had a low number of individuals with good PS but with dependence in ADL/IADL, and a high number of patients with poor PS with some dependence in ADL/IADL.

Here, the characteristics related to each MN were represented by the Hb, transfusion demands and the diagnosis of anemia. All of the other disease-related variables were characterized by the logistic regression model as random effects.

The model fitted in this study incorporated the differences between the MN as random effects. These characteristics were related to the pathogenesis and to the treatment of each disease. Thus, the analysis of the data of Groups I, II and III was significant to the mixed logistic regression model that detected the impact of these difficult-to-control variables.

In this group of patients the Hb concentration and the HCT-CI, but not the age or gender, impacted on the PS of elderly patients with MN as assessed by KPS and ECOG. The mixed logistic regression fitted a model that hypothesized an Hb concentration that was critical to poor PS (Table 5). The most important clinical value is that this critical Hb concentration depended on the aggressiveness of the MN and on the HCT-CI.

This Hb concentration should not be extrapolated but, as far as we know, this is the first survey that fitted a model which

Table 5 – The hypothetical hemoglobin concentration for poor performance status and hematopoietic cell transplantation-comorbidity index of patients with myeloid neoplasms.

Groups	HCT-CI				Critical hemoglobin (g/dL) concentration for poor performance status
	0	1	2	$\geq$ 3	
I – PV/ET/CML	9.53	10.52	11.51	12.50	
II – MF	5.61	6.61	7.60	8.59	
III – MDS/AML	11.71	12.70	13.69	14.68	

PV: polycythemia vera; ET: essential thrombocythemia; CML: chronic myeloid leukemia; MF: myelofibrosis; MDS: myelodysplastic syndromes; AML: acute myeloid leukemia; HCT-CI: hematopoietic cell transplantation-comorbidity index.

could comprise functional assessment and comorbidity score, linked by Hb concentration. Thus, it is possible to conclude that anemia and HCT-CI impact on the functionality of elderly with MN, mainly those with AML and MDS.

As illustrated by Table 5, Group III has the highest critical Hb for poor performance. This fact is congruent to the evidence of higher KPS/ECOG sensitivity in patients with AML/MDS than in other MN. Thus, KPS and ECOG are more easily affected by drops in Hb in Group III compared to Groups I and II.

This evidence may be justified, in part, by the fact that, usually, anemia in patients of Groups I and II occurs over a longer period of time than in those of Group III. Hence, adaptive mechanisms can be triggered over time to better preserve the functional autonomy of patients in Groups I and II.

Another important aspect to be considered is that HCT-CI is a score specifically validated in patients with AML/MDS. As far as we know, there are few studies assessing patients with chronic myeloproliferative disorders using this instrument.^{24,25}

All these aspects show the necessity for a process that validates the hypothetical Hb values that are critical to poor performance (Table 5). This process can be designed by comparing the results of this model applied to patients with chronic myeloproliferative disorders using HCT-CI and the Charlson scale,²⁶ for example.

At this time, the Hb values shown in Table 5 should be assumed less as the targets to be reached in patients with MN and more as an alert that drops in Hb affect functionality mainly of patients with AML/MDS and with high HCT-CI.

Functional status assessed employing ADL and IADL was influenced by gender, age, Hb and comorbidities. There was an increasing dependence in daily activities with drops in Hb concentration, increases in HCT-CI, advancing age and for female patients. This evidence may help healthcare professionals provide social support better adjusted to the patient's needs.

As a cross-sectional survey, this study was not designed to analyze other medical procedures. It should be noted that prognostic scores for MF and MDS take into account Hb concentration and transfusion requirements. Thus, the model fitted here surely can be better calibrated in a longitudinal type study.

As an observational study, it was very hard to control each variable in particular those that comprise the logistic regression model with multivariate analysis. This study was not designed to understand the prognostic value of variables that were included. Previous studies pointed out that functionality has been correlated not only to survival but to the quality of life, mainly in elderly patients with MN.²⁷

This paper is the preliminary result of a research aimed at improving the assessment of elderly patients with MN.

Conclusions

The aggregation of ADL and IADL to the KPS and ECOG scales improved the sensitivity and specificity of the functional assessment of elderly with MN, mainly those with AML

and MDS. Age, gender, Hb and comorbidities affected functional status. However, only comorbidities and Hb impacted on PS. The model fitted with KPS/ECOG identified critical Hb concentrations for poor PS which depends on the aggressiveness of the MN and on the HCT-CI. Thus anemia and HCT-CI impacted on the functionality of this group of patients, mainly those with AML and MDS. Patients with AML and MDS were more sensitive in respect to KPS and ECOG compared to other patients with less aggressive diseases.

Conflicts of interest

The authors declare no conflicts of interest.

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