

Parameters detected by geriatric and quality of life assessment in 195 older patients with myelodysplastic syndromes and acute myeloid leukemia are highly predictive for outcome

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ABSTRACT

Myelodysplastic syndromes and acute myeloid leukemia exemplify the complexity of treatment allocation in older patients as options range from best supportive care, non-intensive treatment (e.g. hypomethylating agents) to intensive chemotherapy/hematopoietic cell transplantation. Novel metrics for non-disease variables are urgently needed to help define the best treatment for each older patient. We investigated the feasibility and prognostic value of geriatric/quality of life assessments aside from established disease-specific variables in 195 patients aged 60 years or over with myelodysplastic syndromes/acute myeloid leukemia. These patients were grouped according to treatment intensity and assessed. Assessment consisted of eight instruments evaluating activities of daily living, depression, mental functioning, mobility, comorbidities, Karnofsky Index and quality of life. Patients with a median age of 71 years (range 60-87 years) with myelodysplastic syndromes (n=63) or acute myeloid leukemia (n=132) were treated either with best supportive care (n=47), hypomethylating agents (n=73) or intensive chemotherapy/hematopoietic cell transplantation (n=75). After selection of variables, pathological activities of daily living and quality of life/fatigue remained highly predictive for overall survival in the entire patient group beyond disease-related risk factors adverse cytogenetics and blast count of 20% or over. In 107 patients treated non-intensively activities of daily living of less than 100 (hazard ratio, HR 2.94), Karnofsky Index below 80 (HR 2.34) and quality of life/fatigue of 50 or over (HR 1.77) were significant prognosticators. Summation of adverse features revealed a high risk of death (HR 9.36). In-depth evaluation of older patients prior to individual treatment allocation is feasible and provides additional information to standard assessment. Patients aged 60 years or over with newly diagnosed myelodysplastic syndromes/acute myeloid leukemia and impairments in activities of daily living, Karnofsky Index below 80%, quality of life/fatigue of 50 or over, are likely to have poor outcomes.

Introduction

In older patients with myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML), available treatment options range from best supportive care (BSC) only, to non-intensive chemotherapy or epigenetic therapy (hypomethylating agents (HA): 5-azacytidine, decitabine) to potentially curative, intensive treatment with standard induction chemotherapy (IC) and consolidation including stem cell transplantation (HCT). Although some advances in intensive chemotherapeutic and transplant procedures have been made (e.g. the introduction of reduced intensity conditioning,^{1,2} only a subgroup of patients aged over 60 years are considered fit for induction, and the percentage drops for older individuals.^{3,4} Parameters for allocating treatment include both dis-

ease-specific parameters such as cytogenetics⁵ and new biomarkers,⁶ as well as patient-specific variables such as numerical age, performance status⁷ and comorbidities.⁸ Other patient-related functional parameters likely considered by the physicians making these decisions have not been sufficiently characterized or quantified.⁹ Standardized tests to determine and quantify the degree of *fitness* are now increasingly being studied also in patients with myeloid neoplasias, lending support to their feasibility and valuable additional information¹⁰ to established models of risk prediction. In the latter context, Krug *et al.* have constructed a strong prognosticator for complete remission and early death based on data of 1,400 AML patients (aged >60 years) treated intensively,¹¹ including the following parameters: body temperature, age, *de novo* leukemia *versus* secondary leukemia, hemoglobin, platelet

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count, fibrinogen, serum lactate dehydrogenase. Addressing tumor diversity is often referred to as *personalized cancer care*. In contrast, we aimed to enhance data on novel metrics for non-disease variables also reflecting patient diversity. Therefore, we sought to delineate prognostic variables within a battery of established functional tests¹² at baseline for elderly patients with MDS and AML. The study did not seek to examine leukemia-specific variables or treatment effects on outcome.

Design and Methods

Patients

Our study cohort included all consecutive patients aged 60 years or over with an initial diagnosis of MDS and AML who presented between March 2004 and June 2008 at the University Hospital Freiburg Medical Center for treatment initiation, together with patients seen at the University Medical Centers of Düsseldorf and Dresden in 2006 and 2007. The local ethics committees and institutional review boards approved the study and all patients gave their informed consent. Of the 195 patients, 130 participated in clinical trials described in the *Online Supplementary Appendix*¹³⁻¹⁵ while 65 could not be included.

Instruments

We applied those instruments to assess patient-related factors recommended for a comprehensive geriatric assessment¹² at baseline and again to survivors at six months (*Online Supplementary Appendix*).¹⁵ To capture performance status (Karnofsky Index, KI), each patient's score was placed on a linear scale between 100 (normally active) and 0 (dead), summarizing their ability to perform daily activities. To document the patient functional status, we used assessments of 'activities of daily living' (ADL; Barthel Index) and 'instrumental activities of daily living' (IADL). The Barthel Index is a reliable assessment of a person's mobility and ability to perform daily self-care tasks. According to the Hamburg classification manual, total scores range from 0 to 100, with lower scores indicating greater disability. The IADL scale measures eight complex activities related to independent functioning. The total score ranges from 0 to 8. Scores of less than the maximum in ADL and IADL denote dependency.¹⁶⁻¹⁸

Data from medical records were extracted to identify and tabulate comorbidity according to both the Charlson¹⁹ and the Hematopoietic Cell Transplantation (HCT)-specific Comorbidity Indices (HCT-CI).²⁰ Comorbidity describes any distinct additional clinical entity that has existed or may occur during a patient's clinical course with an index disease (in this case, MDS/AML). The Charlson Comorbidity Index (CCI) is the most commonly used in oncology. Its main limitation is that the data address only the 19 conditions listed in the index. The HCT-CI presents a comorbidity score adapted to the HCT setting. It assigns points for 17 common medical conditions relevant in the transplant setting, resulting in a score ranging from 0 to 29.

Further geriatric syndromes were assessed by the 'Get-up and Go Test', a brief assessment of gait and balance in older patients. A score of over 20 seconds (s) implies a relevant impairment in mobility.²¹ The Geriatric Depression Scale (GDS) is a self-reporting questionnaire designed specifically to screen for depression in older adults. A score higher than 5 suggests depression.²² The Mini-Mental State Examination (MMSE) is the most widely used instrument for assessing cognitive function, providing a total score that reflects the individual's level of cognitive function.^{23,24} To assess QOL, we used the EORTC QLQ C-30 version 3.0, as this has shown good psychometric utility in evaluating physical QOL

aspects and associated symptomatology.²⁵⁻²⁷ The questionnaire contains one subscale for global quality of life, 5 functioning subscales and 9 symptom subscales, with all subscales linearly converted to a scale from 0 to 100. Minimum duration of the entire assessment was 45 min.

In addition, we documented the following disease-related factors and laboratory data: percentage of bone marrow blasts (MDS or AML, according to FAB classification), cytogenetics (in AML as previously described),^{28,29} IPSS in MDS,³⁰ peripheral blood leukocytes and hemoglobin, serum LDH, serum creatinine, creatinine clearance and serum albumin. To minimize the number of missing values, we combined 'adverse cytogenetics (AML)' and 'IPSS int-2/high risk' into one 'poor risk cytogenetics/IPSS' variable.

Statistical analysis

Data were analyzed using SAS software version 9.1. (SAS Institute Inc., Cary, NC, USA). Cut-off points for single variables were chosen after inspecting their distribution among all 195 patients such that a reasonable distribution into two groups could be obtained, i.e. cut-off points near the median and round numbers were used. Overall survival (OS) was calculated as the time from start of therapy to death from any cause, with patients alive being censored at the date last seen alive, and 6 HA patients who finally received HCT being censored at time of transplantation, respectively. The Kaplan-Meier method was used to estimate OS rates over time, and the impact of possible prognostic factors was analyzed with uni- and multivariate Cox's proportional hazards regression models stratified with respect to therapy. The variable selection procedures Backward Elimination (BE) and Forward Selection (FS) were applied. Results are presented as estimated hazard ratios (HR) with accompanying 95% confidence intervals (95% CI), where a value of HR over 1 represents a higher risk for lower OS for the respective patient group.

Univariate analyses represent a first step in the evaluation of the prognostic factors discussed here. We chose two different approaches to construct a prognostic model based on geriatric assessment/quality of life (GA/QOL) variables. First, in order to investigate whether GA/QOL variables provide any prognostic value beyond that of known prognostic factors, such as the percentage of bone marrow blasts, high-risk cytogenetics (AML)/IPSS, performance status and comorbidities, we applied a multivariate model with BE and FS to a set consisting of those variables having a *P* value less than 0.1 in the univariate analysis. Second, to select among the GA/QOL variables, BE and FS were used for the complete set of 15 GA/QOL variables plus Karnofsky Index, HCT-CI, and the Charlson Index. The resulting final model (which is the same for FS and BE) was used to construct a model in which variables remaining in the final model at a significance level of 5% were weighed according to their regression coefficient rounded to the nearest integer. According to the Kaplan-Meier estimation of OS for each score value, risk groups were then classified. As the analysis is based on a population of patients receiving different treatments, the analysis was carried out for subgroups according to treatment.

Results

Baseline application of the geriatric and quality of life assessment

Between January 2004 and June 2008, 223 patients with MDS or AML were prospectively assessed at the start of their respective treatment (median time from diagnosis to

first specific treatment 40 days, range 5-200 days). Twenty-eight patients were excluded because of missing data at baseline or on follow up, and incapacity to sign informed consent; therefore, 195 patients were included in the statistical analysis. Median follow up was 461 days.

Patients' characteristics are listed in Table 1. Briefly, approximately 25% were allocated according to their physicians' recommendations or their own wish to receive only BSC (consisting of transfusions, cytoreduction with hydroxyurea, and antibiotics) and approximately 38% to either HA or standard IC (two-thirds of the latter proceeded to allografting). A third of the patients were diagnosed with MDS and two-thirds with AML (FAB). Median age was 71 years. Of all patients, 67 were impaired in activities of daily living (ADL<100) and only slightly more than 50% had a performance status (Karnofsky Index) over 80.

Cognitive impairment or signs of overt depression were present in 17 and 28 patients, respectively, and 108 patients required more than 20 s for the 'Get-up and Go Test' (median 21 s) indicating an increase in the risk of falls. Patients had a mean of 0.96 comorbidity index points according to the Charlson Index and 2.5 according to the HCT-CI (Sorrer), respectively. The prognostic factor analysis according to the risk index defined by Wheatley *et al.*³¹ (cytogenetic group, age, white blood count, performance status and type of AML, i.e. *de novo*, secondary) reveals that the majority of trial patients (63.6%) were in the poor risk group and that none of the non-intensively treated patients were in the good risk group (Table 1).

There was a significant difference in initial GA/QOL assessment results among the different treatment groups, with IC patients being markedly younger and significantly less often affected by geriatric symptoms. (Table 1, and *Online Supplementary Table S1*).

Among variables which appeared to be of prognostic importance ($P<0.1$) in univariate analyses, pathological ADL and increased 'fatigue' (≥ 50 by EORTC QLQ-C30) remained highly predictive for overall survival in the entire patient group (BSC, HA, IC/HCT) beyond the established, disease-related risk factors such as poor risk cytogenetics/IPSS and bone marrow blast count of 20% or over. Furthermore, these parameters differentiated convincingly between high- and low-risk patients treated with BSC or HA, with those with a higher score in 'fatigue' and ADL impairments having shorter overall survival. To focus on a homogeneous cohort, and to avoid the confounding effect of treatment, we subjected the GA/QOL values of the 107 patients treated non-intensively (BSC and HA) to further statistical analyses.

Results of the univariate analysis of all tested variables in patients treated non-intensively ($n=107$) are shown in Table 2. We performed multivariate analysis after variable selection. The final model that included the established disease-related risk factors 'poor risk cytogenetics/IPSS' and 'bone marrow blasts' is shown in Table 3. The final model (which included only GA/QOL variables) revealed the strong prognostic information of impaired performance defined as Karnofsky Index below 80, ADL below 100 and 'fatigue' of 50 or over by EORTC QLQ C-30, as shown in Table 4. These parameters differentiated strongly between patients treated with BSC alone or HA, with those showing signs of dependence (ADL, Karnofsky Index), or with a fatigue score of 50 or over indicating shorter overall survival (Figure 1A-F).

Application of a risk assessment score

To obtain a simple risk assessment score in patients treated non-intensively which predicted a decrease in overall survival, we combined the variables 'performance status' (Karnofsky Index), 'activities of daily living' (ADL) and 'QOL/fatigue'. Because the regression coefficients were similar in size, no further weighting was necessary. Both disease-related parameters (bone marrow blasts $\geq 20\%$ and poor risk cytogenetics/IPSS) that had revealed no significant association (Fisher's Exact Test; *Online Supplementary Table S2*) were not included in the final model, as we sought parameters not primarily reflecting disease status.

Application of this score to patients treated without curative intent (BSC and HA) is shown in Figure 2A. Patients considered at low risk (with 0 risk features) had significantly longer overall survival (median 774 days) than patients with 1 or 2 points (median 231 days) having intermediate risk, and than the high-risk group (median 51 days) with three risk features ($P<0.0001$). In the next step, the score was applied to patients that had been allocated to the three different treatment categories. As shown in Figure 2B and C, this score highly discriminates the outcome in patients allocated to either BSC and HA, respectively. Application of the score to IC/HCT patients is shown in Figure 2D.

Table 5 shows some associations between the risk assessment score and established scores, where the majority of patients are found to be within the poor prognosis risk group according to Wheatley *et al.*

Discussion

A rationale for incorporating a geriatric assessment into the management of older cancer patients is to obtain additional objective, quantifiable and reproducible information on the individual beyond the physician's clinical judgment alone.^{32,33} These patient-specific data have recently been more closely considered when estimating treatment tolerance and outcome. Assessments are recommended for screening purposes, and to eventually be followed by focused interventions in a geriatric oncology setting,^{34,35} yet there is still no firm evidence of the clinical impact of this approach with regard to its predictive value on mortality.³⁶ However, an association has been reported between GA outcomes and treatment allocation in elderly cancer patients.³⁷

In this study, patients were prospectively assessed by a multidimensional geriatric and QOL assessment to demonstrate its applicability in a multicenter setting (a prerequisite for its further application in larger trials). Furthermore, it was our aim to investigate whether elderly MDS/AML patients with differing prognoses can be identified based on patient-related information. While highly valuable, the GA entails administering a battery of instruments that is resource-intensive. This reinforced our efforts to define the strongest prognosticators to briefly objectify what so far has been a largely subjective matter of treatment allocation.³⁸

Initial GA/QOL values differed significantly among the three treatment groups. As expected, patients 'fit for induction allografting' displayed the best result. This confirms that the adopted criteria may already be influencing the rigorous therapeutic decision-making process, and that

pendent patient-related prognostic parameters suited to developing a prognostic model. In the multivariate analysis of overall survival in 107 patients, only impairments in performance status, in activities of daily living (ADL) and the symptom item 'fatigue' from the EORTC QOL-C30 were retained as independent prognostic factors of overall survival, in addition to the known MDS/AML-related risk factors poor risk cytogenetics/IPSS and bone marrow

blasts of 20% or over. Therefore, the basic information reflecting a patient's functionality (KI, ADL) and QOL strongly indicate vulnerability and complement the key clinical parameters that have until now influenced treatment decision-making (i.e. numerical age, percentage of blast or cytogenetics). Impairments in the more sophisticated parameters (IADL, MMSE, 'Get-Up-and-Go Test') may on the contrary represent a distinct individual state

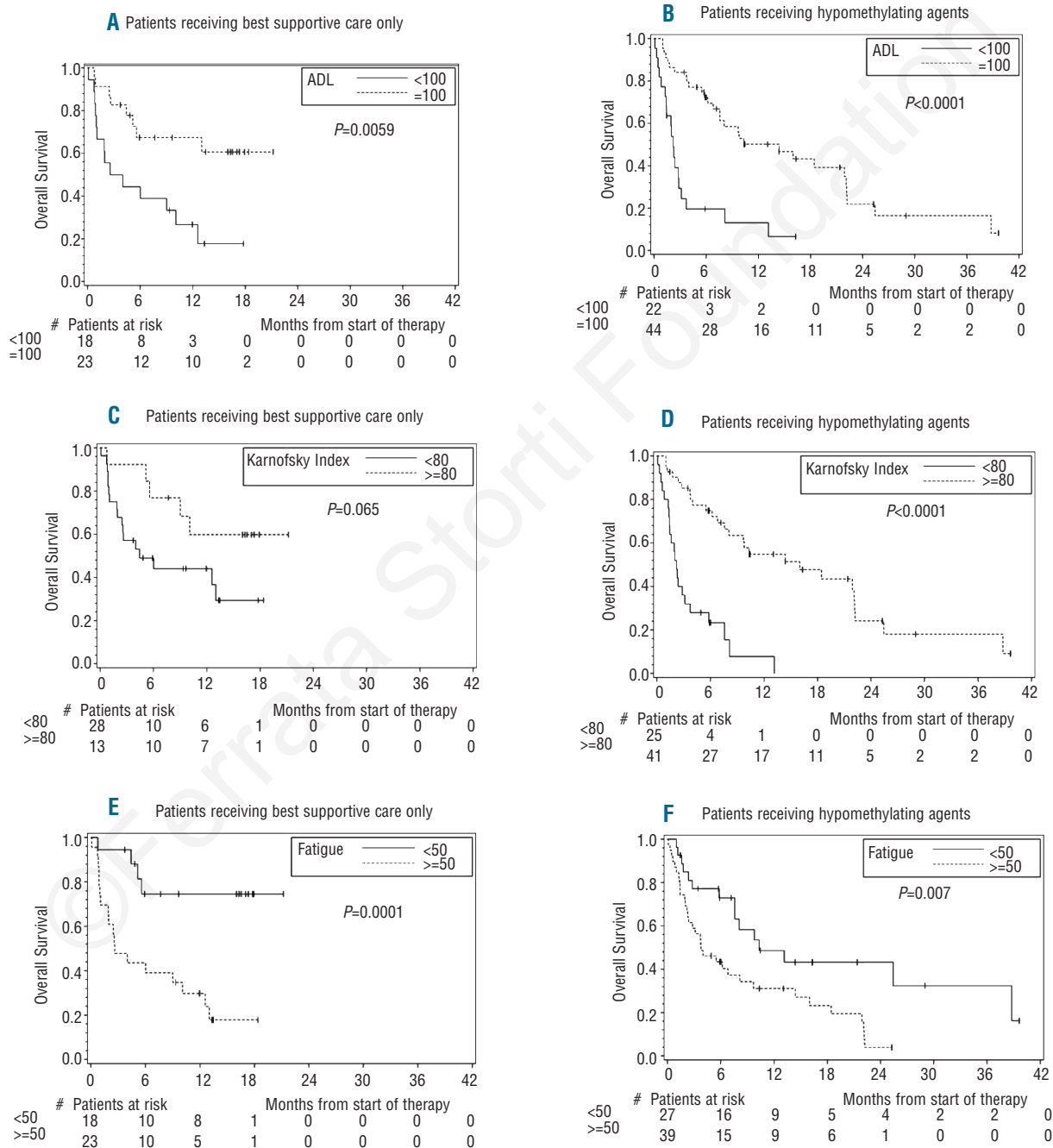


Figure 1. Overall survival (OS) of non-intensively treated patients according to the geriatric assessment results for activities of daily living (ADL) (A,B), performance status (Karnofsky Index <80) (C,D), and 'fatigue' <50 (E,F). (A). Patients receiving best supportive care only. (B). Patients receiving hypomethylating agents. (C). Patients receiving best supportive care only. (D). Patients receiving hypomethylating agents. (E). Patients receiving best supportive care only. (F). Patients receiving hypomethylating agents.

and may, therefore, be more suited to focused geriatric screening and intervention.

Focusing on the single most important risk parameters of our study, the Karnofsky Index is as frequently used to describe performance as is the ECOG performance status. Both show excellent correlation and interconversion. Only recently, the Karnofsky Index has been shown to identify patients with at least two abnormalities on the GA.³⁹ To reassess our findings on the prognostic power of performance status, we compared data with those of a randomized phase III EORTC trial of low-dose decitabine *versus* BSC in elderly patients with intermediate- or high-risk

myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy.⁴⁰ These independent data of 137 evaluable patients confirmed the prognostic value of PS (HR 2.70; *P*=0.005 for PS<80) as shown in *Online Supplementary Tables S3 and S4*.

The ADL or Barthel Index comprises 10 activities of daily living with different levels of dependency.¹⁶ It has been suggested that this is more sensitive than the Karnofsky Index for assessing physical functioning in some patient groups but it has not yet been investigated as a potential prognosticator in patients with hematologic neoplasias.⁴¹ As opposed to the performance indices that reflect the physicians' estimation, ADL requires detailed information in a standardized questionnaire. Interestingly, despite correlations between ADL and Karnofsky Index, ADL does provide additional information, as both parameters were retained in our multivariate analysis. This easily obtainable index, used frequently in daily practice to

Table 2. Univariate analysis of tested variables (non-intensive treatment groups; n=107). Hazard Ratios (HR) and confidence intervals (95% CI) were estimated using Cox's proportional hazards regression models. Categorical variables were applied.

Parameter	Hazard Ratio (95%CI)	P value
Patient-related factors		
Karnofsky Index <80%	4.24 (2.41, 7.46)	<0.0001
ADL (Barthel Index) <100	4.00 (2.39, 6.62)	<0.0001
Timed "up+go" test >30 sec.	3.30 (2.00, 5.42)	<0.0001
Instrum. activities of daily living	1.97 (1.22, 3.18)	0.006
Mini mental state (MMS) examination<28	1.92 (1.18, 3.11)	0.008
HCT-Cl (Sorrer) comorbidities≥3	1.67 (1.05, 2.68)	0.03
Charlson comorbidities >1	1.64 (1.00, 2.67)	0.05
Timed "up+go" test >20 sec.	1.41 (0.85, 2.33)	0.19
HCT-Cl (Sorrer) comorbidities ≥1	1.21 (0.64, 2.25)	0.56
Age ≥73 years	1.14 (0.71, 1.82)	0.59
Geriatric Depression Scale (GDS) ≥6	1.08 (0.53, 2.18)	0.84
EORTC QLQ-C30 domains		
Physical functioning<50	3.13 (1.89, 5.18)	<0.0001
Fatigue ≥50	3.03 (1.77, 5.17)	<0.0001
Role functioning<50	2.68 (1.61, 4.44)	0.0001
Cognitive functioning<50	2.58 (1.27, 5.23)	0.009
Global QOL<50	2.44 (1.51, 3.92)	0.0002
Emotional functioning<50	1.86 (1.15, 3.0)	0.01
Nausea/vomiting≥0	1.70 (1.02, 2.81)	0.04
Pain≥0	1.67 (1.05, 2.65)	0.03
Social functioning <50	1.64 (0.36, 1.03)	0.06
Dyspnea≥0	1.25 (0.75, 2.08)	0.39
Disease-related factors		
Bone marrow blasts >20%	4.06 (2.21, 7.45)	<0.0001
Poor risk cytogenetics/IPSS	2.03 (1.21, 3.39)	0.007
WBC >3x10 ⁹ /L	1.42 (0.88, 2.28)	0.15

Table 5. Relationship of scores.

Risk assessment score	BSC/HA (n=107)		HCT-Cl (Sorrer) IC (n=75)		Total (n=182)	
	Median	Range	Median	Range	Median	Range
Good (score 0)	1.5	0-6	1.5	0-7	1.5	0-7
Standard (score 1-2)	2	0-7	2.5	0-8	2.0	0-7
Poor (score 3)	3	0-7	3.0	0-6	3.0	0-7

Risk assessment score	BSC/HA (n=73)		Wheatley Score IC (n=67)		Total (n=140)	
	Median	Range	Median	Range	Median	Range
Good (score 0)	9.5	9-14	8.5	5-12	9	5-14
Standard (score 1-2)	10.5	10.5-15	9.5	6-15	10	6-15
Poor (score 3)	10	10-15	7	6-10	10	6-15

Table 3. Multivariate analysis results for parameters with P<0.1 in univariate analysis, including established disease-related risk factors "poor risk cytogenetics/IPSS" and blasts (n=107), using a dummy variable "Risk Status unknown" in 14 cases.

Parameter	Hazard Ratio (95%CI)	P value
BM Blasts: > 20% <i>vs.</i> ≤20% or unknown	3.39 (1.82, 6.33)	0.0001
Cytogenetics/IPSS: Poor <i>vs.</i> low risk	3.04 (1.69, 5.46)	0.0002
ADL (Barthel Index): <100 <i>vs.</i> 100	2.60 (1.37, 4.93)	0.004
Karnofsky Index: <80 <i>vs.</i> ≥80	2.14 (1.10, 4.15)	0.02
HCT-Cl (Sorrer): ≥3 <i>vs.</i> <3	1.98 (1.14, 3.44)	0.02
EORTC QLQ-C30 fatigue: ≥50 <i>vs.</i> <50	1.82 (1.02, 3.23)	0.04
Cytogenetics/IPSS: unknown <i>vs.</i> low risk	1.86 (0.69, 4.98)	0.22

Table 4. Multivariate analysis results for GA/QOL parameters only, with P<0.1 in univariate analysis, excluding risk factors "poor risk cytogenetics/IPSS" and blasts (n=107). Remaining variables define "Risk Assessment Score".

Parameter	Hazard Ratio (95%CI)	P value
Karnofsky Index<80	2.45 (1.23, 4.87)	0.01
ADL (Barthel Index) <100	2.10 (1.13, 3.89)	0.02
EORTC QLQ-C30 Fatigue ≥50	2.09 (1.17, 3.71)	0.01

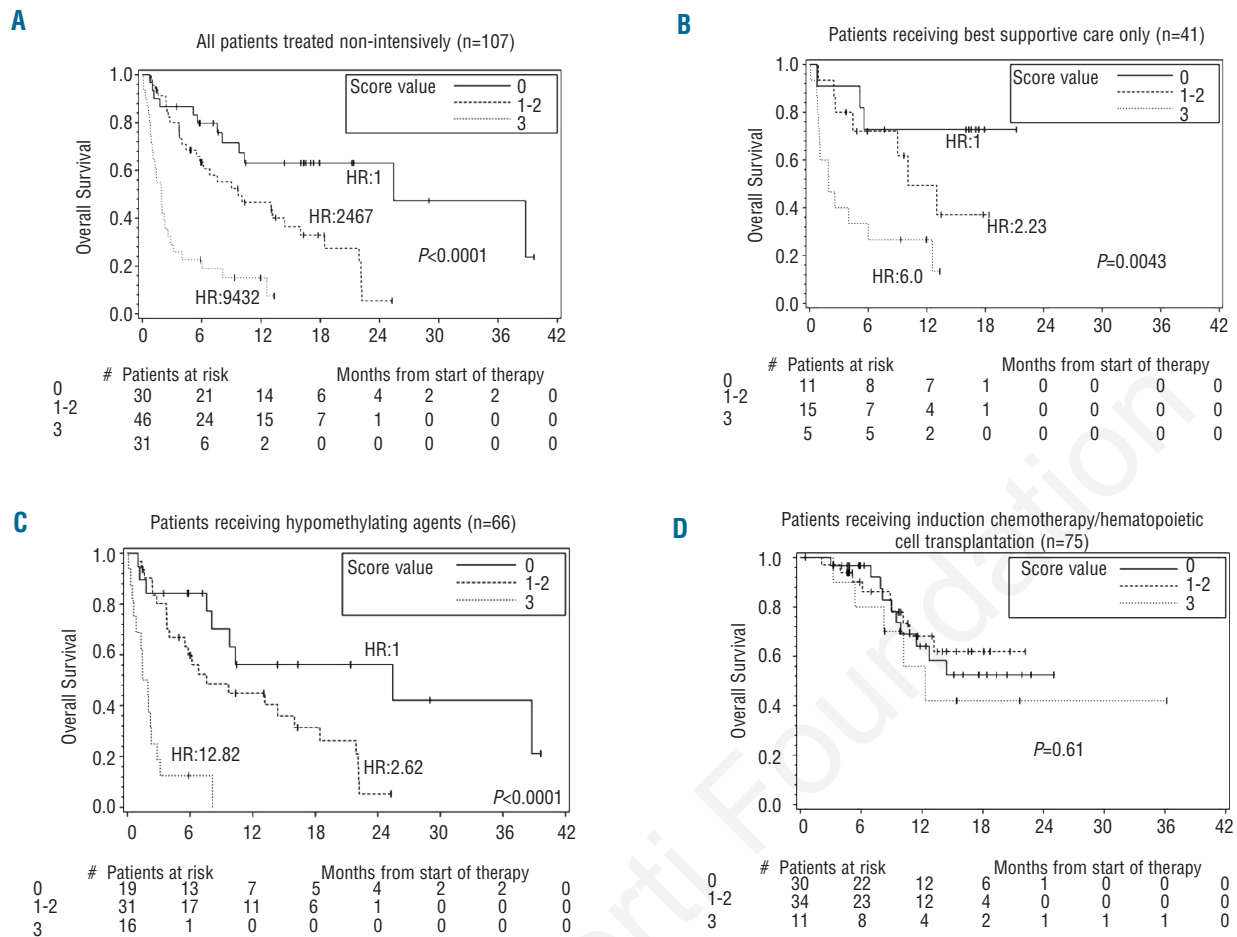


Figure 2. Overall survival (OS) according to frailty score risk groups and treatment (evaluable patients) (A). All patients treated non-intensively (n=107). (B). Patients receiving best supportive care only (n=41). (C). Patients receiving hypomethylating agents (n=66). (D). Patients receiving induction chemotherapy/hematopoietic cell transplantation (n=75).

estimate and communicate degrees of dependence, emerges in this study as having additional value in objectifying decision-making processes. In agreement with this, a recent investigation on the impact of a geriatric assessment in treatment decision-making in elderly patients revealed that the ADL's value correlates with treatment allocation (non-intensive care vs. intensive treatment efforts).³⁷

Several studies have shown baseline QOL parameters to be independent prognostic factors in different malignancies⁴²⁻⁴⁵ underscoring the assumption that QOL scales add prognostic information to clinical measures and predict survival.⁴⁶ Patient ratings of physical symptoms (i.e. 'fatigue'), physical functioning and global health status/QOL have repeatedly been the best predictors of survival.^{45,47} In this context, Oliva *et al.* reported a study on elderly AML patients in which QOL physical functioning was of prognostic relevance yet, somewhat surprisingly, did not correlate to the physician-assessed ECOG performance status.⁴⁸ While the item 'fatigue' has been shown to be prognostically relevant in several different malignant diseases,^{47,49-51} so far only hypotheses to explain the mechanisms underlying the association between reported data on patient health status and duration of survival have been proposed.⁵² 'Fatigue' is a patient-reported

outcome and multi-faceted concept including both mental and physical components whose critical domains have not been sufficiently standardized and for which several scales have been developed.⁵³ Despite these shortcomings, we believe that further investigation of this extremely debilitating symptom observed in many if not all cancer patients is useful for optimizing patient care.

When comparing our score to established risk assessment scores (i.e. comorbidity score by Sorrow, risk index by Wheatley), we found that, despite some associations, independent and complementary information could be obtained. We, therefore, suggest that the scores do actually measure different aspects of patient- and disease-specific factors. Possibly, the estimation of functionality might display an increasing relevance in patients treated non-intensively who are, on average, older, while parameters calculated in the established scores may be even more relevant in younger, intensively treated patients. Future studies may reveal whether the scores can complement each other.

Our study has several limitations. First, the assessments were all performed by a small number of trained physicians raising the possibility that a bias could have been introduced. However, the instruments were, whenever possible, patient self-administered. Second, our patient

population was heterogeneous and included patients with different treatment intensities. However, this is an observational study that sought to determine the prognostic value of the QOL/GA at baseline. The study did not seek to examine disease-specific variables or treatment effects on outcomes and, therefore, risk prediction models were carried out according to treatment. The resulting risk assessment score revealed the best prognostic potency for patients treated non-intensively and will need further validation.

In conclusion, this study supports the systematic, prospective use of geriatric and QOL assessments as important additional tools in clinical evaluations. It raises awareness of relevant issues of QOL as well as objective functional capabilities that might otherwise go unnoticed. Some scales within the comprehensive GA showed weak prognostic impact and strong correlations to other parameters, suggesting the use of a brief and simplified tool. In particular, patients' functional and symptom variables as measured by Karnofsky Index, ADL and 'fatigue' appear to possess prognostic strength similar to that of MDS/AML-related risk factors, such as poor risk cytogenetics/IPSS and blast counts. Patients aged 60 years or over with newly diagnosed MDS/AML and a Karnofsky Index below 80%, EORTC QOL fatigue of 50 or over, and impairments in ADL are likely to have poor outcomes. Prospective studies to validate our findings are well under-

way. Finally, data on a validated unique score reflecting the reserves or vulnerability of this special patient population are needed to incorporate them into algorithms for therapeutic decision-making to complement established disease-specific risk factors; a very worthwhile step toward defining the best treatment option for each older patient.

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