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Malnutrition in Older Patients With Hematological Malignancies at Initial Diagnosis – Association With Impairments in Health Status, Systemic Inflammation and Adverse Outcome

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Abstract

Poor nutritional status is a common problem in cancer patients at advanced age, but the prevalence and impact of malnutrition in hematological malignancies remains underinvestigated. To evaluate nutritional status in older adults over age 70 with newly diagnosed hematological malignancies, we enrolled 147 patients and assessed weight loss, food intake, Mini Nutritional Assessment (MNA), and BMI. We compared nutritional status with demographic data, inflammation markers, and restrictions in multidimensional geriatric assessment. MNA classified 43% of patients being at risk of, and 15% having manifest malnutrition. A moderate/severe decrease in food intake was reported by 24% or 16%, a recent weight loss of 1 to 3 kg or >3 kg by 19% or 31%, and a BMI <23 kg/m^2 by 29%. Lowered serum albumin (<3.5 g/dL) was prevalent in 14% of patients, and in 38% Glasgow Prognostic Score indicated hyperinflammation. Principal component analysis clustered malnutrition with inflammation markers and pronounced impairments, that is, fatigue, depression, comorbidities, reduced functional capacities. Severe decrease in food intake (HR: 3.3 (1.9–5.8), $p < 0.001$), >3 kg weight loss (HR: 2.3 (1.4–3.9), $p = 0.001$), impaired MNA (HR: 2.8 (1.3–6.2), $p = 0.010$), and low serum albumin (HR: 2.1 (1.1–4.0), $p = 0.030$) were significantly associated with shortened overall survival. Recent weight loss >3 kg (HR: 2.2 (1.1–4.3), $p = 0.022$), and low BMI (HR: 3.3 (1.8–6.0), $p < 0.001$) remained independent adverse parameters in multivariate Cox proportional hazard regression analyses. Malnourishment at initial diagnosis is frequent in older patients with hematological malignancies and represents an adverse prognosticator. Clustering of malnutrition with impairments and systemic inflammation suggests an underlying common pathway.

Introduction

Poor nutritional status is a frequent condition that affects medical outcomes. Advanced age is a recognized risk factor for poor nutritional status. Malnourishment becomes even more relevant in patients with cancer because both the malignant disease and its treatment are detrimental for nutritional status.[1,2] Thus, poor nutritional status is common in elderly cancer patients and is assumed to contribute to many adverse events including impaired quality of life, functional decline, reduced tolerance of cancer treatment, and increased mortality.[3–5] Reflecting the relevance of weight loss and cachexia in multimodal care of cancer patients, several experts have developed recommendations for the assessment and management of malnutrition in older cancer patients.[1,4,6] However, presence of malnutrition is still often poorly recognized and underestimated in clinical practice.[1]

Hematological malignancies represent typical diseases of advanced age. In fact, several of the most frequent subtypes, namely non-Hodgkin's lymphoma (NHL), acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), and multiple myeloma (MM), are characterized by a median age of >70 years at diagnosis.[7,8] When therapy is ultimately initiated, most patients are, in fact, a few years older. Based on population aging and demographic changes predicted for the next years, we need to anticipate a continuous increase in the number of elderly patients with hematological malignancies. A growing number of treatment options, including cytotoxic chemotherapy, monoclonal antibodies, immune-modulatory

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drugs or small molecules, have become available over the past years. Thus, individualized care in elder persons requires a structured evaluation that should integrate patient centered factors, including nutritional status.[6,8]

Despite the medical relevance in evaluation and care, data on the frequency and the clinical consequences of malnutrition in blood cancer are so far rare. The goal of this study was to assess the prevalence and clinical relevance of patients at risk for malnutrition in a cohort of older patients with a hematological malignancy at initial diagnosis before start of cancer-specific therapy. Moreover, we analyzed the clustering of malnutrition with hyperinflammation and with impairments as defined by MGA.

Methods

Patients and geriatric assessment

In a single-institution cohort study, patients at the Department of Internal Medicine V (Hematology and Oncology), Innsbruck Medical University Hospital newly diagnosed with hematological malignancies completed a multi-dimensional geriatric assessment (MGA) at initial diagnosis before the start of cancer-specific treatment. The enrollment of patients is shown in Supplement 1 (Supplemental Digital Content, http://links.lww.com/HS/A59).

Evaluation of malnutrition was performed by using items from G8 questionnaire. Based on the high prevalence and the severity of impairments, Mini Nutritional Assessment (MNA) was introduced additionally during the study to get a more precise description of malnourishment. Details of the different evaluations performed are given in the CONSORT diagram (Supplement 1, Supplemental Digital Content, http://links.lww.com/HS/A59). Malnutrition was defined as more than 3 kg weight loss over the last 3 months, decline in food intake over the last 3 months, and by BMI status $<23\,kg/m^2$. These parameters have been categorized based on definitions of G8,[9] MNA,[10] and in accordance with adaptions for persons at advance age.[11]

The MGA followed the concept described elsewhere[12,13] and included instrumental activities of daily living (IADL), the 30-item Geriatric Depression Scale (GDS-30), Mini Mental State Examination (MMSE), and Charlson Comorbidity Index (CCI). We assessed fatigue with the EORTC Quality of Life Core 30 questionnaire as described by Efficace et al.[14]

Baseline data comprised demographic data, WHO performance status (WHO-PS), and laboratory parameters including serum ferritin, serum albumin, and C-reactive protein (CRP), and the modified systemic inflammation-based modified Glasgow Prognostic Score (mGPS).[15] Hematological malignancies included AML, MDS, myeloproliferative neoplasms (MPN), NHL, both aggressive and indolent. (Table 1). We base the classification of treatment modalities into standard vs attenuated on the definition by Hamaker et al.[16] (see Supplement 2, Supplemental Digital Content, http://links.lww.com/HS/A59, for details). Four patients died before treatment decision and were excluded from Cox proportional hazard regression.

Patients from the 70th year of life and older, and without a previous history of other cancers, were eligible. The local ethics committee approved the study and we enrolled only patients able to sign the informed consent.

Statistical analyses

Categorization of all parameters followed published cut-offs, or laboratory standards respectively (see Tables 1 and 2). Based on definitions of G8[9] and MNA,[10] and in accordance with adaptions for persons at advance age,[11] we used $\geq 23\,kg/m^2$ as a cut-off for BMI. For hazard ratios, we dichotomized BMI categories using this cut off, as the additional BMI categories defined in G8[9] and MNA,[10] that is, <19, and ≥19–21, contained very low patient numbers (6 and 10, respectively). Thresholds for laboratory parameters followed published cut-offs of $\leq 3.5\,g/dL$ for serum albumin,[17] and the reference limits given by the analyzing laboratory, $> 4.02\,g/dL$ serum albumin; $\leq 0.5\,mg/dL$ for CRP; and $> 400\,\mu g/L$ for serum ferritin. We compared means and frequencies of each parameter at baseline and additionally the frequency in the subcategories low BMI and considerable weight loss (>3 kg). We used the crosstab function in SPSS to test whether there is an association between categorical variables (depending on variable type, Chi square, linear by linear association, Kendall's tau).

For all parameters included in the univariate COX model, we performed a principal component analysis (PCA)[18,19] to visualize the relationship between the parameters. We entered data as continuous parameters if available, that is, for BMI, age, serum albumin, CRP, serum ferritin, CCI, GDS-30, MMSE, and IADL. High scores on the same axis, that is, principal component, characterize strong associations (see Supplement 3, Supplemental Digital Content, http://links.lww.com/HS/A59, for more details). Parameters located closer together are more strongly associated. In contrast, parameters plotting in opposite directions reflect opposing trends. The tip of the arrow marks the maximum of a gradient. The lowest value of a gradient is not reflected by the intersection of the 2 axes but by the opposite direction of the arrow. We tested the significance of the PCA axes by bootstrapping broken stick method. The percentage mentioned with the axes is the proportion of the variability in the patient data that is explained by each axis.

Survival analyses

We measured overall 2-year survival from the date of assessment to the date of death from any cause or 2 years whichever occurred first, thus the 57 patients surviving to 2 years were censored at this point. No patients were lost to follow-up within the first 2 years. We analyzed the impact of each parameter on overall 2-year survival via Kaplan-Meier methods and assessed significant differences with log-rank tests. We used a multivariate Cox proportional hazard regression to analyze the hazard ratio of each parameter that is clinically meaningful, and independent of each other based on independency tests and also the PCA, to avoid autocorrelation. Thus, BMI and weight loss as indicators of nutritional status, but not appetite loss, serum albumin, or MNA as those were associated with BMI or weight loss. We included mGPS, which combines CRP and serum albumin. We excluded Mini Nutritional Assessment as it had much smaller patient numbers due to the later onset of MNA (see Table 2 and Supplement 1, Supplemental Digital Content, http://links.lww.com/HS/A59). In order to limit the number of variables in the multivariate model, we omitted GDS30 from the multivariate model that was not significant in the univariate model. We confirmed that the proportional hazard ratio assumption was not violated following the suggestions by Delgado et al.[20] The proportional hazard assumption remained valid when using time-dependent covariates. We tested the interaction terms "treatment times age" and "treatment times diagnosis" which both did not become significant in the multivariate analyses.

We performed survival analyses and independency tests using IBM SPSS Statistics, Version 24. Principal component analyses

Table 1

Characteristics of patients, and prevalence of low BMI, weight loss, mGPS and fatigue at baseline.

	Total		BMI < 23 kg/m²			Weight loss > 3kg		
Variables	**n**	**%**	**n**	**(%)**	**p**	**n (%)**		**p**
Entire Cohort	147		42			45		
Sex					**0.016**			**0.036**
Female	68	46%	26	38%		15	22%	
Male	79	54%	16	20%		30	38%	
Age					0.460			0.119
<70 years	4	3%	1	25%		3	75%	
70–79 years	86	59%	23	27%		28	33%	
80–89 years	52	35%	15	29%		14	27%	
>90 years	5	3%	3	60%		0	0%	
Subtypes					**0.020**			0.079
Non-Hodgkin's lymphoma indolent	13	9%	5	38%		1	8%	
Non-Hodgkin's lymphoma aggressive	33	22%	8	24%		15	45%	
Myeloproliferative neoplasms	10	7%	7	70%		2	20%	
Myelodysplastic syndromes	43	29%	13	30%		13	30%	
Acute myeloid leukemia	48	33%	9	19%		14	29%	
Hematological therapy					0.826			0.963
Standard therapy	121	82%	34	2%		37	3%	
Attenuated therapy	22	15%	6	27%		7	32%	
Unknown/died before decision	4	3%	2	50%		1	25%	
Overall 2-year survival								
Alive	57	40%	10	18%		11	19%	
Dead	90	60%	32	36%		34	38%	
WHO Performance Status	147				0.488			0.801
<2	88	59%	26	30%		27	31%	
2	50	34%	15	30%		16	32%	
>2	9	7%	1	11%		2	22%	
BMI	147							0.579
<23 kg/m²	42	29%				31	33%	
≥23 kg/m²	105	71%				14	30%	
Weight loss during the last 3 months	147				0.063			
no decrease	66	45%	13	20%				
1–3 kg	28	19%	12	43%				
does not know	8	5%	3	38%				
>3 kg	45	31%	14	31%				
Modified Glasgow Prognostic Score (mGPS)	136				**0.033**			0.290
0 (CRP ≤ 1 mg/dL)	85	62%	19	22%		22	26%	
1 (CRP > 1 mg/dL or albumin <3.5 g/dL)	39	29%	17	44%		13	33%	
2 (CRP > 1 mg/dL and albumin <3.5 g/dL)	12	9%	2	17%		5	42%	
Fatigue	147				0.834			0.120
no / mild fatigue (<45)	82	56%	24	29%		21	26%	
minor or strong fatigue	65	44%	18	28%		24	37%	

For each subcategory, we show how many individuals, and which proportion, have a BMI <23 kg/m², or have lost > 3 kg over the last 3 months (eg, of 68 females, 15 (22%) had lost more than 3 kg over the last 3 months). Classification of weight loss and food intake is based on G8 and MNA. Classification of fatigue is based on EORTC QLQ-C30. Bold numbers emphasize significant associations of variables with BMI, or weight loss resp. in test of independence or trend ($p < 0.05$).

were calculated with Canoco5.[21] We tested the significance of the PCA axes with a the broken stick model implemented in the software "R" by the Package "rijoja".[22]

Results

Patient characteristics

The 147 patients were included in this analysis. Median age was 78 years (range 67–98 years). The majority of patients were in the group of 70 to 79 or 80 to 89 years (59% and 35%, respectively). Median overall survival time was 13 months with a range from 0 to 93 months and an overall survival at 2 years of 39.6%. Impaired WHO-PS ≥2 was observed in 41% and geriatric impairments >3 in about one-third of individuals (Table 1).

Prevalence of malnutrition

A recent unintentional weight loss of 1 to 3 kg or >3 kg was detected in 19% and 31% of patients, respectively. A weight loss of >3 kg was more often observed in male patients ($p = 0.036$) and in individuals with low food intake ($p < 0.001$), or low serum albumin levels ($p = 0.002$) (Tables 1 and 2). A moderate or severe decrease in food intake at initial presentation was reported by 24% and 16% of patients. Six (4%) patients revealed a BMI of < 19 kg/m²; 10 (6.8%) ≥19 yo <21; and 26 (17.7%) ≥21 to <23, and 105 (71.4%) individuals ≥23 kg/m². A BMI <23 kg/m² was

Table 2

Nutritional status compared to laboratory markers of inflammation and restrictions in geriatric evaluation.

	Total		BMI <23 kg/m^2			Weight loss >3 kg		
Parameters	**n**	**%**	**n**	**(%)**	**p**	**n**	**(%)**	**p**
BMI	147		42			45		0.063
<23 kg/m^2	42	29%				14	33%	
≥ 23 kg/m^2	105	71%				31	30%	
Weight loss during last 3 months	147				0.063			
no decrease	66	45%	13	20%				
1–3 kg	28	19%	12	43%				
does not know	8	5%	3	38%				
>3 kg	45	31%	14	31%				
Food intake during last 3 months	147				0.155			**<0.001**
no decrease	89	60%	21	24%		16	18%	
moderate decrease	35	24%	11	31%		16	46%	
severe decrease	23	16%	10	43%		13	57%	
Mini Nutritional Assessment (MNA)	83				**0.007**			**<0.001**
well nourished	35	42%	3	9%		4	11%	
at risk for malnutrition	36	43%	14	39%		20	56%	
malnourished	12	15%	5	42%		4	33%	
Modified Glasgow Prognostic Score (mGPS)	136				**0.033**			0.290
0 (CRP $\leq$ 1 mg/dL)	85	62%	19	22%		22	26%	
1 (CRP $>$ 1 mg/dL or albumin <3.5 g/dL)	39	29%	17	44%		13	33%	
2 (CRP $>$ 1 mg/dL and albumin <3.5 g/dL)	12	9%	2	17%		5	42%	
Serum albumin	118				0.347			**0.003**
>4.02 g/dL	66	56%	17	26%		11	17%	
3.5–4.02 g/dL	36	30%	14	39%		15	42%	
<3.5 g/dL	16	14%	4	25%		8	50%	
C-reactive protein (CRP)	147				0.075			0.121
$<$ 0.5 mg/dL	55	63%	11	20%		13	24%	
$\geq$ 0.5 mg/dL	92	37%	31	34%		32	35%	
Serum ferritin	144				0.783			0.932
≤ 400 µg/L	78	54%	20	26%		24	31%	
>400 µg/L	66	46%	22	33%		20	30%	
Fatigue	147				0.834			0.120
no / mild fatigue (<45)	82	56%	24	29%		21	26%	
minor or strong fatigue	65	44%	18	28%		24	37%	
Instrumental activities of daily living (IADL)	147				0.213			0.704
>6 female, $=5$ male	102	69%	26	26%		33	32%	
≤ 6 female, ≤ 4 male	45	31%	16	36%		12	27%	
Geriatric Depression Scale (GDS 30)	147				0.902			0.783
<10	113	77%	32	28%		34	30%	
≥ 10	34	23%	10	29%		11	32%	
Mini Mental State Examination (MMSE)	147				0.452			0.912
no dementia	121	82%	33	27%		37	31%	
moderate/severe dementia	26	18%	9	35%		8	31%	
Charlson Comorbidity Index (CCI)	147				0.332			0.771
<3	111	76%	34	31%		35	32%	
≥ 3	36	24%	8	22%		10	28%	

For each subcategory, we show how many individuals, and which proportion, have a BMI <23 kg/m^2, or have lost >3 kg over the last 3 months (eg, of 42 patients with a BMI <23 kg/m^2, 14 (33%) had lost more than 3 kg over the last 3 months). The modified Glasgow Prognostic Score (mGPS) assigns a score of zero to all patients with CRP ≤ 1 mg/dL, that is, also for patients with albumin <3.5 mg/dL, thus effectively as long as CRP is not elevated independently of albumin. This allows the inclusion of patients with a low CRP but no measurement of serum albumin. Classification of fatigue is based on EORTC QLQ-C30. MNA started at a later time point during the study; thus, the number of patients enrolled is lower than for other scores. In male individuals IADL-5 was applied, which omits the items cooking, household and laundry. MMSE: only one patient suffered from severe dementia. Serum albumin cut-off 3.5 g/dL is based on Akirov et al,[16] 4.02 g/dL is the lower reference value used in the local laboratory. Bold numbers emphasize significance ($p<0.05$) in independency/trend test, thus parameters dependent of BMI or weight loss, respectively.

thus observed in 29% of patients and was more frequently detected in women ($p=0.016$; Table 1). A considerable proportion of individuals were at risk of malnutrition (43%) or malnourished (15%) as defined by MNA. Hypalbuminemia <3.5 g/dL was observed in 14% of patients. Laboratory evaluation revealed elevated biomarkers of inflammation, namely CRP and serum ferritin, in 37% and 46% of the cohort, respectively. mGPS indicated a pronounced systemic inflammation with a score of 1 in 29% of the patients, and a score of 2 in 9% of patients. MGA revealed impairments in instrumental activities (31% of patients), in mood (23%) and in cognition screening (18%). We observed severe comorbidities as defined by CCI in 24% of the patients. Almost half of the patients (44%) reported moderate or strong fatigue (Table 2).

Principal component analysis

The PCA (Fig. 1) demonstrates the association between age, sex, diagnosis, nutritional status, inflammation, and impairments as defined by MGA. PCA Axis 1 (principal component 1)

explains 17% of the variability in the patient data. PCA Axis 2 explains an additional 10%. Despite the relatively low values, both axes are significant when tested with a bootstrapping broken-stick method.

We observed a distinct clustering of malnutrition with systemic inflammation and impairments (Fig. 1, Supplement 3, Supplemental Digital Content, http://links.lww.com/HS/A59). Malnutrition, in particular a weight loss of >3 kg and a severe decrease in food intake, were strongly linked to restrictions and hyperinflammation. Patients with a profound weight loss and strongly decreased food intake tended to have a high CRP, low albumin, and consequently elevated mGPS. iii) They were inclined to suffer from fatigue and depression (GDS30), had a reduced WHO-PS, and advanced comorbidities (CCI), and had impaired scoring both in IADL and MMSE. The first principal component (x-axis) thus reflects an increase in impairments (Fig. 1).

The second PCA axis (y axis) mainly reflects differences between female and male patients: female patients tended to lose 1 to 3 kg and to have a moderate decrease in food intake, while male patients tended to have a higher BMI at initial diagnosis.

The short length of the arrows attributed to the type of hematological malignancies indicates that diagnosis type was not strongly associated with a particular impairment, rather that impairments occur across all malignancies.

Impact of nutritional status on clinical outcome

To analyze the impact of various parameters on clinical outcome, we performed a univariate Cox regression analysis (Table 3). Impaired food intake, recent weight loss, low BMI, and malnourishment in MNA were significantly associated with

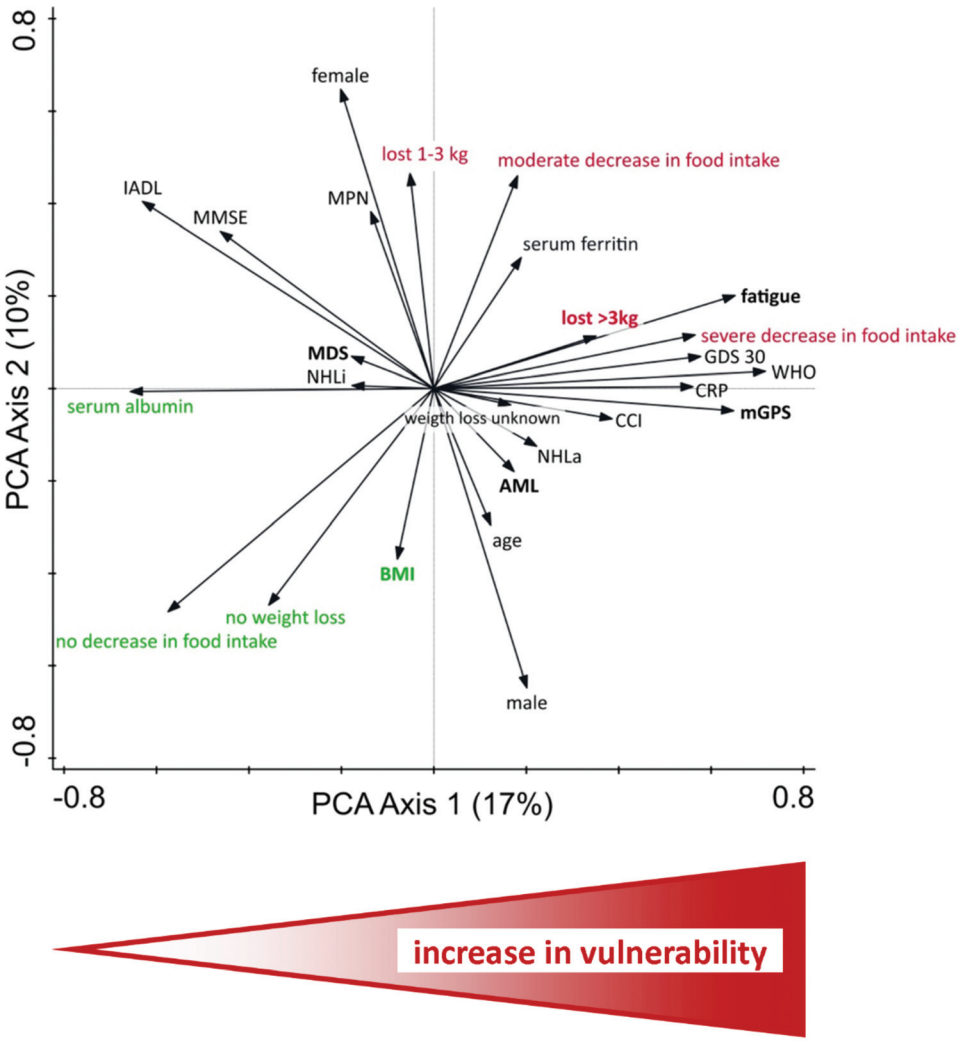

Figure 1. Principal component analysis (PCA) visualizing the pattern and interrelations of patient characteristics including age, sex, diagnosis, nutritional status, inflammation markers, and geriatric assessment scores at baseline (see Tables 1 and 2, Suppl. Table 1, http://links.lww.com/HS/A59). Parameters located closer together are more strongly associated (eg, high CRP and high CCI score, or severe decrease in food intake and fatigue). In contrast, parameters plotting in opposite directions reflect opposing trends (eg, severe decrease in food intake versus high serum albumin). For association of parameters, see also Supplement 3. The tip of the arrow marks the maximum of a gradient. Note that parameters indicative of a higher vulnerability are located to the right (gradient indicated at bottom), whereas variables associated with better health status are located on the left. Parameters of malnutrition are shown in red (located in the top right section), whereas items of good nutritional status are in green (lower left section). Parameters that are independent predictors for OS are shown in boldface. We used absolute values for all parameters except those only available as categories (weight loss, decrease in food intake, diagnosis, mGPS). Treatment was not included in this analysis, as this parameter does not impact baseline conditions.

shortened overall survival at 2 years (Table 3, Fig. 2). Moreover, elevated CRP and serum ferritin levels, low serum albumin and a score of 2 in mGPS, were adverse predictors for clinical outcome. In addition, marked comorbidities, pronounced fatigue and restrictions in MGA, namely in functional capacities and in cognition, correlated with an adverse clinical course. Aggressive NHL and myeloid neoplasms had a more adverse prognosis than indolent NHL. We observed the most unfavorable outcome in patients with AML and MDS (Table 3).

For the multivariate analysis, we considered the following parameters: sex, age, subtypes of malignancy, treatment modality, WHO performance status, BMI, weight loss, mGPS, serum ferritin, fatigue, IADL, MMS and CCI. Weight loss >3 kg (hazard ratio (HR) 2.2; confidence limits (CL) 1.1–4.3), and low BMI (HR 3.0; CL 1.8–6.0) remained predictive for 2-year survival (Table 3). Likewise, diagnosis AML (HR 6.9; CL 1.5–30.7), diagnosis MDS (HR 5.7; CL 1.3–25.9), an mGPS of 2 (HR 2.8; CL 1.2–6.7), fatigue (HR 2.4; CL 1.4–4.2), and attenuated treatment (HR 2.6; CL 1.1–5.8) stayed independently prognostic (Table 3).

Discussion

Malnutrition in older cancer patients not only adversely affects quality of life, but is also associated with modification of the initial treatment plan, poor treatment outcome, and increased adverse events.[1,4] To our knowledge, this is the first prospective study of nutritional status, defined by several parameters in parallel, including correlations between malnutrition and impairments and clinical outcome, in a cohort of older patients with hematological malignancies at initial diagnosis.

Table 3

Prognostic parameters for overall survival in univariate and multivariate Cox regression analyses.

	Univariate analysis				Multivariate analysis			
	HR	95% CL		p value	HR	95% CL		p value
Baseline variables								
Female sex	0.8	0.5	1.2	0.227	0.7	0.4	1.2	0.202
Age (absolute)	1.0	0.99	1.1	0.071	1.0	0.99	1.1	0.127
Diagnosis (compared to NHLi)				**0.013**				**0.024**
NHLa	**4.5**	**1.1**	**19.5**		2.6	0.5	12.7	
MPN	**5.1**	**1.0**	**25.2**		4.0	0.7	21.6	
MDS	**5.7**	**1.3**	**24.0**		**5.7**	**1.3**	**25.9**	
AML	**8.7**	**2.1**	**36.0**		**6.9**	**1.5**	**30.7**	
Attenuated therapy	**5.3**	**2.3**	**12.2**	**<0.001**	**2.6**	**1.1**	**5.8**	**0.024**
WHO Performance Status (compared to WHO 0)				**0.010**				0.561
WHO 1	**1.6**	**1.0**	**2.5**		0.7	0.3	1.5	
WHO 2	**2.8**	**1.3**	**5.9**		0.5	0.1	2.0	
Nutritional status								
BMI <23 kg/m^2	**1.9**	1.2	2.9	**0.005**	**3.3**	**1.8**	**6.0**	**<0.001**
Weight loss during last 3 months (compared to no loss)				**0.002**				0.063
1–3 kg	**2.1**	1.2	3.7		1.7	0.8	3.3	
>3 kg	**2.3**	1.4	3.9		**2.2**	**1.1**	**4.3**	
Food intake over last 3 months (compared to no decrease)				**<0.001**				
moderate decrease	**1.9**	**1.2**	**3.1**		NI			
severe decrease	**3.3**	**1.9**	**5.8**		NI			
Mini Nutritional Assessment (compared to not at risk)				**0.035**				
at risk for malnutrition	1.6	0.9	3.1		NI			
malnourished	**2.8**	**1.3**	**6.2**		NI			
Markers of inflammation								
Modified Glasgow Prognostic Score (compared to mGPS 0)				**0.001**				**0.044**
mGPS 1	1.3	0.8	2.1		1.0	0.5	1.8	
mGPS 2	**3.6**	**1.8**	**7.0**		**2.8**	**1.2**	**6.7**	
Serum albumin (compared to >4.02 g/dL)				0.084				
3.5 - 4.02 g/dL	1.4	0.8	2.3		NI			
< 3.5 g/dL	**2.1**	**1.1**	**4.0**		NI			
C-reactive protein	**1.1**	**1.0**	**1.1**	**0.002**	NI			
Serum ferritin >400 µg/L	**1.8**	**1.2**	**2.85**	**0.006**	1.6	0.9	2.6	0.082
Geriatric impairments								
Fatigue moderate/strong	**2.3**	**1.5**	**3.5**	**<0.001**	**2.4**	**1.4**	**4.2**	**0.001**
IADL (female ≤6, male ≤4)	**2.0**	**1.3**	**3.1**	**0.001**	1.7	0.7	4.3	0.238
GDS-30 ≥ 10	1.3	0.8	2.1	0.233	NI			
MMS ≤ 24	**1.7**	**1.1**	**2.8**	**0.033**	0.9	0.4	2.0	0.728
CCI ≥ 3	**1.6**	**1.0**	**2.6**	**0.039**	1.3	0.7	2.5	0.370

For details on different parameters, see footnote to Table 2. Comparison of parameters with 2 categories: male compared to female; standard therapy versus attenuated therapy (see Supplement 2); or below respectively above the cut off value mentioned for each parameter. Age and C-reactive protein was entered as continuous variable. Serum albumin, and C-reactive protein were excluded in the multivariate model as both are parameters of mGPS. Decrease in food intake, and MNA were not included in the multivariate model as they are not independent of BMI or weight loss based on Chi square analysis. Furthermore, as MNA was started at a later time point during the study, its inclusion would result in the exclusion of 40% of the patients in a multivariate analysis. Bold numbers emphasize variables with a HR with lower CL > 1 and/or significance ($p < 0.05$). Interaction terms tested in addition (age * treatment, treatment * diagnosis) did not become significant. HR: hazard ratios. CL: confidence limits. NI: not included.

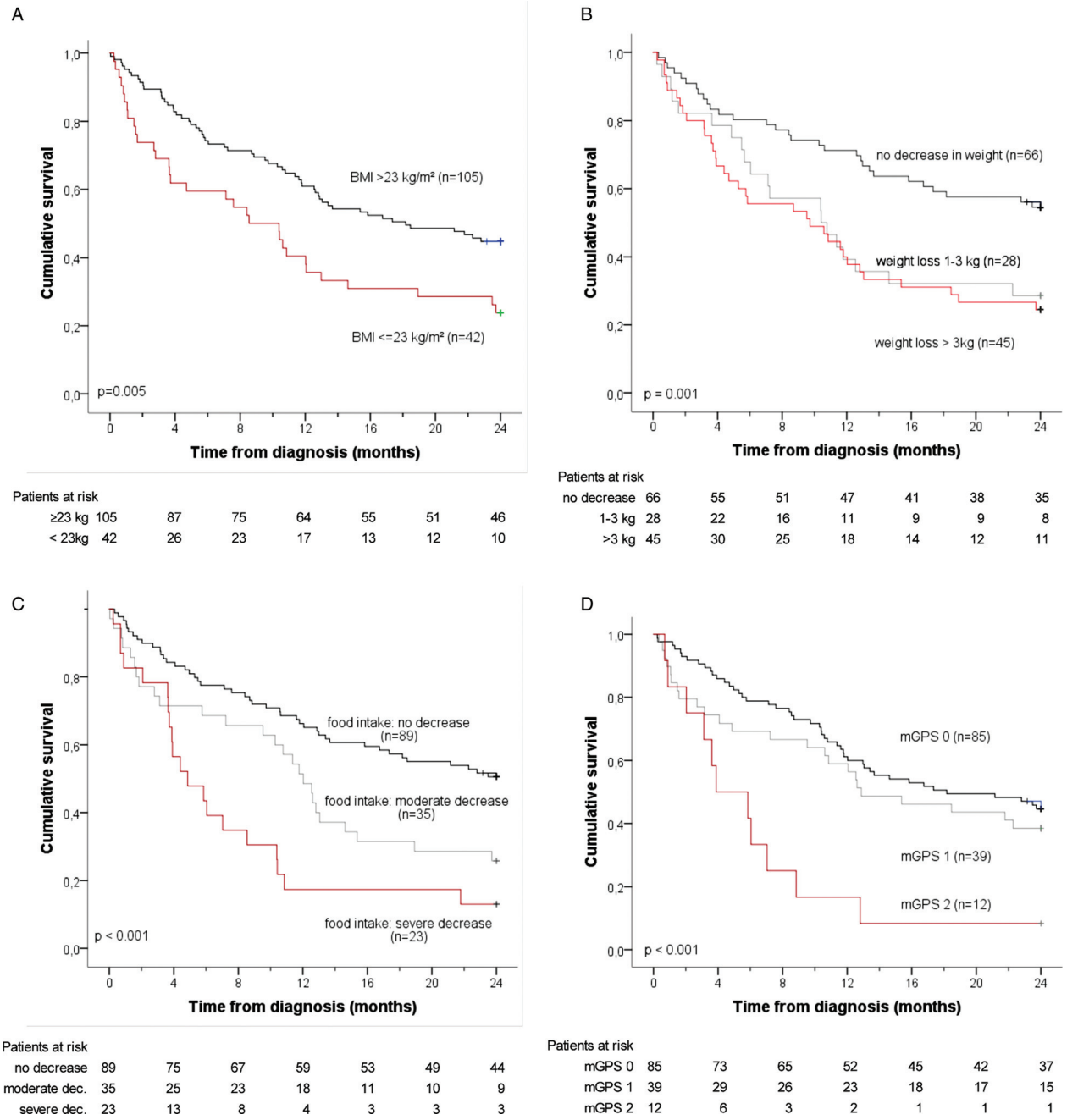

Figure 2. Overall survival according to baseline patient's nutritional and inflammation status. A) BMI, B) weight loss, C) food intake; D) modified Glasgow Prognostic Score (mGPS). Patients with good nutritional status and low inflammatory markers had a significantly higher probability of survival over the first 2 years (see Table 3). For number of events see supplement 4. p values from log rank test.

The high prevalence of malnourishment in patients freshly diagnosed with hematological malignancies, is an essential finding in this study. We observed a pronounced unintentional weight loss in 31%, decreased food intake in 40%, decreased serum albumin levels in 14%, and risk for malnutrition or manifest malnourishment in MNA in 43% and 15% of individuals. These results are in accordance with the prevalence of malnutrition in solid tumors, which ranges from 20% to over 70% in many studies, with differences related to patient age, cancer type and stage.[1,2] Previous analyses of malnutrition associated with malignant hemopathies revealed that nearly half of patients suffer from nutritional impairments[5]. However, data on hematological malignancies at initial diagnosis are still rare or hampered by later assessment during the disease course,[9,23–26] rather than at initial diagnosis.[27] Moreover, most cohorts focused on the evaluation of impact of nutritional status on tolerance of therapy, namely for CHOP poly-chemotherapy in NHL,[28–30] or for hematopoietic stem cell transplantation (HSCT),[24,31] resulting in a pronounced selection bias. In addition, most studies included solid tumors,[9,23,25,32,33] which prevents a valid conclusion regarding the clinical relevance of nutritional status in hematological malignancies. This prospec-

tive observational study thus adds substantial information on the prevalence and severity of malnutrition in older persons with hematological malignancies at initial presentation. Our data emphasize the need for screening for malnutrition and of nutrition assessment at an early stage of the disease to identify and prevent malnutritionby nutritional interventions in this group of patients.[1,4]

The observation that parameters of nutritional assessment, namely BMI and weight loss, remained independent prognostic parameters for survival underlines the clinical relevance of nutritional status. While several studies demonstrated that nutritional parameters significantly explain clinical outcome in univariate analyses,[1,4,5] few of these parameters stayed independently predictive in multivariate analyses.[27,28,30] This is reflected in the PCA performed in our study: several of the nutritional parameters, namely weight loss, decreased food intake, low serum albumin, increased mGPS scores, clustered in the PCA, thus indicating that they are very closely related. This phenomenon consequently causes redundancy and auto-correlation when analyzed in parallel in multivariate analyses.[19] The prognostic relevance of different histological subtypes and treatments and of self-reported fatigue in this study extends data from the literature for older individuals with hematological malignancies.[12–14] This study thus emphasizes the relevance of an exact diagnosis, and the inclusion of patients' perception and perspective for prognostication and individualized decision making.[7,34]

The classification of malnutrition traditionally relies on low BMI and weight loss. Thresholds for BMI used in this study deserve a comment: limits in the literature are not uniform and are often based on the WHO definition for younger individuals and may explain the lack of prognostic impact of BMI in the literature.[1] Importantly, for older individuals, Winter et al[11] identified a BMI $<23\,kg/m^2$ as a significant predictor of increased mortality. Using this threshold in our study, patients with a lower BMI revealed a more unfavorable outcome. Thus, at advanced age, this BMI threshold should be considered for inclusion in hematological malignancies. Weight loss was defined in this study as an absolute decline over the past 3 months as defined by G8-scoring.[32] The evaluation of percent weight loss (% WL) as suggested by Martin et al.[35] may be considered as a valid parameter in future studies. Based on global obesity, an assessment based on weight is considered to be insufficient and should be complemented by an evaluation of food intake and a change in weight loss.[1]

Cancer-related malnutrition is a multifactorial process. An underlying inflammatory condition has been postulated to be essential in cancer-associated biologic changes, including anorexia, sarcopenia, and frailty.[1,36] The clustering of malnutrition with biomarkers of inflammation, explicitly the Glasgow Prognostic Score, with impairments, namely in mood, performance status, increased fatigue and comorbidities in this study indicates that targeting systemic inflammation may be an essential therapeutic possibility.

As cancer-associated malnutrition can only be partially reversed by conventional nutritional support, several approaches to inhibit inflammation have been suggested.[1] Ongoing clinical studies aim at reducing systemic inflammation in ageing, cardiovascular disease and frailty by means of non-steroidal anti-inflammatory drugs (NSAID) or new pharmacological treatments that affect signaling pathways. The therapeutic efficacy of the IL-1b blocking antibody canakinumab in the CANTOS trial proves the relevance of this concept.[37] The potential of this approach is underlined by the observation that somatic mutations and inflammatory processes may play a causal role in increased comorbidities, and reduced nutritional and health status in hematological malignancies.[36,38]

While the heterogeneity of hematological malignancies included is a limiting factor in this study, it allows for conclusions on the general relevance of our observations for hematological malignancies. Still, further studies should focus on disease-specific analyses. Another restraint is the limited number of patients with MNA analyses which hampers the full evaluation of this score within our cohort. The relevance of mGPS to assess the inflammatory response in this study deserves a comment: mGPS has so far been applied and validated in over 30,000 patients with different cancer subtypes.[15] Likewise, mGPS has been used in several studies[39–42] in non-Hodgkin lymphomas, whereas the evidence for validity in leukemias is lacking so far. Strengths of this study are the parallel and prospective assessment of several scores in a single-institutional setting, and the comparison with a full geriatric assessment.

In conclusion, we detected a high prevalence of malnutrition in older persons with hematological malignancies at initial diagnosis. Malnutrition clusters with hyperinflammation and impairments, namely with fatigue, restrictions in depression scoring, reduced functional capacities and pronounced comorbidities several parameters were independently prognostic for survival. These results emphasize the relevance of a structured assessment of nutritional status, and the need for individualized interventions to improve the nutritional status. Analyses of underlying inflammatory mechanisms may form the basis for rational therapeutic options.

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