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Malnutrition Predicts Clinical Outcome in Patients with Neuroendocrine Neoplasia

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Key Words
Neuroendocrine neoplasia · Malnutrition · Nutritional status · Bioelectrical impedance analysis · Outcome · Progressive disease · Chemotherapy · Survival · Prognosis

Abstract
Malnutrition is a common problem in oncological diseases, influencing treatment outcomes, treatment complications, quality of life and survival. The potential role of malnutrition has not yet been studied systematically in neuroendocrine neoplasms (NEN), which, due to their growing prevalence and additional therapeutic options, provide an increasing clinical challenge to diagnosis and management. The aim of this cross-sectional observational study, which included a long-term follow-up, was therefore to define the prevalence of malnutrition in 203 patients with NEN using various methodological approaches, and to analyse the short- and long-term outcome of malnourished patients. A detailed subgroup analysis was also performed to define risk factors for poorer outcome. When applying malnutrition screening scores, 21–25% of the NEN patients were at risk of or demonstrated manifest malnutrition. This was confirmed by anthropometric measurements, by determination of serum surrogate parameters such as albumin as well as by bioelectrical impedance analysis (BIA), particularly phase angle α. The length of hospital stay was significantly longer in malnourished NEN patients, while long-term overall survival was highly significantly reduced. Patients with high-grade (G3) neuroendocrine carcinomas, progressive disease and undergoing chemotherapy were at particular risk of malnutrition associated with a poorer outcome. Multivariate analysis confirmed the important and highly significant role of malnutrition as an independent prognostic factor for NEN besides proliferative capacity (G3 NEC). Malnutrition is therefore an underrecognized problem in NEN patients which should systematically be diagnosed by widely available standard methods such as Nutritional Risk Screening (NRS), serum albumin assessment and BIA, and treated to improve both short- and long-term outcomes.

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Introduction

Disease-related malnutrition is a frequently encountered yet underrecognized clinical phenomenon in patient care with substantial prognostic and socioeconomic implications for affected patients and caregivers [1–8]. This is particularly true for patients with solid neoplasms [9, 10] such as lung [11, 12], gastric [10, 13, 14], pancreatic [14, 15], colorectal [14, 16, 17], ovarian [18–20] or breast cancers [16]. Consequences resulting from malnutrition include increased complication rates after oncological surgery, an increased duration of hospitalization mostly due to a higher number of infectious complications, increased side effects of cytotoxic treatment, a decreased response to treatment, a poorer quality of life and ultimately a worse prognosis in malnourished cancer patients [7, 9, 12, 14, 21–25]. Thus, both regular nutritional assessment and nutritional therapy have been recommended to cancer patients with active disease or undergoing resective surgery to improve their clinical outcome [9, 26, 27].

Neuroendocrine neoplasms (NEN) compose a heterogeneous tumour entity which is relatively infrequent; however, an increase in both incidence and – probably due to relatively good long-term survival rates – prevalence has been noted during the last few years [28–31]. NEN arise mostly in the gastroenteropancreatic system and the bronchial tract, but in rare cases they also occur in the ovaries, the urinary bladder and other organs [28, 30]; the most prominent localities within the gastroenteropancreatic system are the small bowel and the pancreas [28, 32]. According to the WHO classification of 2000, NEN are classified as well-differentiated neuroendocrine tumours (WDET; when non-metastatic) or as well-differentiated neuroendocrine carcinomas (WDEC; when metastatic or grossly invasive), while less well-differentiated, more aggressive tumours were termed poorly differentiated endocrine carcinomas (PDEC) [33]. Importantly, NEN are heterogeneous not only with respect to the organ of origin and their cellular differentiation but also with respect to their proliferative behaviour [32, 34–37]. Thus NEN are also classified as grade 1 (G1) or grade 2 (G2) neuroendocrine tumours (NET) if their proliferative index is either below 3% (G1) or between 3 and 20% (G2); G1/2 NET largely correspond to WDET/C [38]. Cases in which the proliferative index (determined by immunohistochemical staining for nuclear Ki-67 protein expression) is higher than 20% are now classified as grade 3 (G3) neuroendocrine carcinomas (NEC) and correspond in most cases to PDEC [30].

A hallmark of NEN, particularly G1/2 NET or WDET/C, is their ability to produce and secrete either gastroenteropancreatic hormones or biogenic amines [30]. Various hormone hypersecretion syndromes such as the carcinoid syndrome or the hyperinsulinaemic hypoglycaemia syndrome of insulinomas therefore characterize the clinical course in 30–40% of the affected patients [30, 32]. However, approximately 60% of the patients never develop such a syndrome and thus have non-functioning NET/C [30, 39, 40]. Although considered a rare disease, during the last years a number of prognostic risk factors have been identified for NEN, including TNM stage, Ki-67 grade, chromogranin A positivity and others depending on the studied cohorts [32, 34–37, 41]. Clinically important endpoints such as quality of life or nutritional status have, however, been studied only very limitedly [42] or non-systematically [34, 41]. Poor nutritional status as reflected in a body mass index (BMI) below normal has been reported to influence outcome in patients receiving transcatheter arterial chemoembolization [41] or in patients with pancreatic NET [34]; however, no further details on nutritional status in correlation with disease parameters or clinical outcome were reported for these highly selective study cohorts.

Currently, nutritional status assessment is based on various methods, usually representing a composite endpoint reflecting a patient's metabolic state – in the case of malnutrition, the result of catabolic drivers overriding anabolic mechanisms [9, 43–45]. These methods include clinical assessments such as the Subjective Global Assessment (SGA) [46] or Nutritional Risk Screening (NRS) [47], which now represent the most commonly applied nutritional status assessment tools in clinical practice. Anthropometric measurements include not only measurements of height and body weight and the combination of both as the BMI but also mid-upper arm circumference (MUAC) and triceps skinfold thickness (TST) as surrogates of malnutrition-associated loss of muscle mass or subcutaneous fat deposits [48]. Body composition can in addition be assessed by bioelectrical impedance analysis (BIA), which essentially measures resistance to an electrical current and extrapolates fluid and fat compartments from this [4, 5, 23, 43], thereby assessing malnutrition-associated patterns of body composition such as increased extracellular mass (ECM), which is largely defined by extracellular water, and decreased body cell mass (BCM) [49]. Other methods of assessing nutritional status have been the measurement of several circulating serum proteins such as albumin or transferrin as surrogates

of protein turnover [5, 50] or the combination of albumin with body weight as the Nutritional Risk Index (NRI) [24, 51]. Ultimately, all these methods have proven valid in assessing malnutrition in the general population and in oncological patients in particular, and have been correlated with overall survival of the specific patient groups studied [5–7, 10, 17, 18, 20, 47, 52–56].

The aim of this study was – for the first time in NEN – to systematically assess nutritional status and the prevalence of malnutrition in patients with NEN using clinical scores, anthropometry, BIA and serum surrogate parameters in a cross-sectional design and to correlate the results with tumour-specific characteristics and long-term outcome as assessed by routine follow-up visits of the patients. Thereby, we assessed the specific role of malnutrition for prognosis and patient management in this highly specific, heterogeneous and clinically challenging tumour entity of NEN.

Subjects and Methods

Between 2006 and 2008, nutritional status was routinely assessed in 203 consecutive patients with histologically confirmed NEN when presenting to our clinical unit as inpatients (n = 177) or outpatients (n = 26). Reasons for admission were staging examinations, therapeutic interventions or follow-up visits. All patients were 18 years or older, had a histopathological confirmation of the NEN and had consented to nutritional status assessment performed as part of the routine clinical assessment.

Patient and Tumour Characteristics

Patient-specific information included age, gender, height, current body weight, recent weight changes and date of initial diagnosis of the NEN. Tumour-specific information such as primary tumour localization, Ki-67 grade, TNM stage at initial diagnosis and at presentation, pattern of metastasis, presence or absence of a hormone hypersecretion syndrome and concurrent therapies was recorded. For inpatients, the duration of their stay in the hospital at the time of nutritional status assessment [length of hospital stay (LoS)] was also recorded. For survival analysis, the time between the date of nutritional status assessment and death or last patient contact was obtained.

Screening Scores

The SGA was performed according to Detsky et al. [46], and the NRS [47] as has been recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) [43]. With the SGA, patients were classified as well nourished (SGA A), moderately or suspected malnourished (SGA B) and severely malnourished (SGA C). With the NRS, patients achieving a score of ≥3 were considered at high risk of malnutrition as opposed to those with a score of 0 [patients with complete remission (CR) or no residual disease] to 2 (patients with manifest NEN all had at least a score of 1 due to active tumour disease).

Anthropometry

For anthropometric determination, body height was measured without shoes using a stadiometer (seca 220; seca, Hamburg, Germany) to the nearest 0.5 cm. Actual body weight was determined using an electronic scale (seca 910; seca) to the nearest 0.1 kg. From these results, the BMI was calculated (kilogram weight per height in metres squared). MUAC and TST were measured on the non-dominant arm; MUAC was determined in the middle between the olecranon and the acromion using a non-elastic tape measure, and TST was assessed using a skinfold calliper (Holtain LTD, Crymych, UK).

Bioelectrical Impedance Analysis

BIA was performed using the whole-body tetrapolar contact electrode approach; an alternating electric current of 800 μA at 5, 50 and 100 kHz was applied and measured with the Nutriguard-M device (Data Input GmbH, Darmstadt, Germany). An implanted cardiac pacemaker or defibrillator device was considered an absolute contraindication to BIA (as was pregnancy), due to theoretically possible interactions caused by the small currents applied during BIA measurements. The patients were positioned in supine position, and two pairs of current-introducing and voltage-sensing electrodes (Bianostic Classic; Data Input GmbH) were attached to the back of the hand of the dominant side of the body and the ipsilateral foot after having cleaned the attachment sites with a disinfecting solution (Softasept N; B. Braun Melsungen AG, Melsungen, Germany) at predefined locations [5, 57]. Resistance (R) and reactance (X_c) were measured and documented; the phase angle α (°) was calculated as has been reported [58]. Total body water (TBW) was calculated as $0.69 \times H^2/R + 0.8$ and fat-free mass (FFM) as TBW/0.732. BCM was calculated as FFM × 0.29 × ln (°) [59, 60].

Serum Surrogate Parameters

Blood samples for serum albumin and transferrin measurement were routinely drawn when clinically appropriate and measured in the central clinical chemistry laboratory using photometry for albumin and immunoturbidimetry for transferrin. Normal reference values were 3.60 g/dl for albumin and 200–360 mg/dl for transferrin. The NRI was calculated from serum albumin concentrations in relation to any recent weight loss according to the formula NRI = 1.519 × serum albumin (g/l) + 0.417 × (current weight/usual weight) × 100; by this, the NRI is a composite score of a serum surrogate parameter (albumin), an anthropometric parameter (body weight) and the recent history of body weight changes [61].

Statistical Analysis

Statistical evaluation was performed using SPSS software version 20.0 (SPSS GmbH, Munich, Germany). All values are given as means ± standard deviation. All metric values were tested for normal distribution using the Kolmogorov-Smirnov test and further analysed using the paired t test. Non-normally distributed metric variables and ordinally scaled variables were analysed using the Wilcoxon-Mann-Whitney test. For nominally scaled variables, the χ^2 test and Fisher's exact test were applied. Univariate analysis of overall survival was performed using the Kaplan-Meier method and tested for significance using log-rank testing. Multivariate analysis of potentially independent prognostic factors was performed using the Cox proportional-hazards model. A p value of <0.05 was considered to be statistically significant.

Table 1. Patient characteristics and screening score results according to primary tumour location

Primary tumour location	n (%)	Age, years	Sex M/F	WDET/WDEC/PDEC	G1/G2/G3	Stage I–IIIA (LD)/ stage IIIB–IV (ED)	SGA		NRS	
							A	B + C	1–2	≥3
Total	203 (100)	63.4	98/105	20/160/18	66/106/19	24/168	152	51	159	44
Lung	12 (5.9)	66.2	6/6	3/9/0	0/12/0	3/8	8	4	10	2
Stomach (sporadic)	7 (3.4)	72.1	4/3	1/3/3	1/1/5	1/6	4	3	4	3
Stomach (ECLoma)	4 (2.0)	60.7	1/3	4/0/0	2/1/0	4/0	3	1	3	1
Duodenum	13 (6.4)	67.1	5/8	2/10/1	10/3/0	6/5	11	2	11	2
Jejunum	5 (2.5)	59.4	3/2	0/5/0	2/2/0	0/5	4	1	4	1
Ileum	50 (24.6)	65.4	21/29	0/49/0	24/23/1	0/50	38	12	40	10
Appendix	5 (2.5)	50.4	0/5	1/3/1	4/1/0	0/4	5	0	5	0
Pancreas	52 (25.6)	61.7	32/20	4/46/2	9/38/3	5/46	36	16	37	15
Rectum	12 (5.9)	64.3	6/6	3/6/2	4/4/2	4/6	11	1	11	1
Cup	27 (13.3)	61.3	11/16	0/19/6	8/12/5	0/26	19	8	20	7
Others[a]	16 (7.9)	61.8	9/7	2/10/3	2/9/3	1/12	13	3	14	2
Missing	0	0	0	5	12	11	0	0	0	0

[a] Including the oesophagus, hepatobiliary region, caecum, colon, ovary, kidney, skin, thyroid gland, sinus sphenoidalis, phaeochromocytoma, adrenal gland, presacral region and papilla of Vater.

Table 2. Disease-specific tumour characteristics (treatments, current growth behaviour: CR/PR/SD/PD)

	n	%
Type of therapy at the time of examination		
Surgery	5	6.4
Chemotherapy	26	33.4
Somatostatin analogues	40	51.3
Yttrium-DOTATOC-PRRT	1	1.3
Interferon	3	3.8
TACE	3	3.8
Total	78	100
Current growth behaviour		
Initial diagnosis	12	5.9
CR	26	12.8
PR	8	4.0
SD	69	34.0
PD	86	42.4
Missing	2	1.0
Total	203	100

TACE = Transcatheter arterial chemoembolization; PRRT = peptide receptor radionuclide therapy.

Results

In 203 patients with histologically proven NEN, nutritional status was acquired and evaluated. The gender distribution was almost even (female: n = 105; male: n = 98), the median age at initial diagnosis of NEN disease was 59 years (mean 57.2, range 7–85), and the median age at nutritional status acquisition was 63 years (mean 60.8). The median follow-up was 44 months (mean 57.6, range 0–250). The distribution of age, gender, tumour classification according to WHO 2000 and Ki-67 grading according to the primary tumour location are given in table 1; TNM staging was divided into two subgroups, namely limited disease (LD), including stages I–IIIA, and extensive disease (ED), including stages IIIB and IV, i.e. grossly metastatic NEN. Metastatic sites were the liver (n = 125; 36%), lymph nodes (118; 34%), bones (23; 7%), peritoneum (20; 6%), lungs (15; 4%), ovaries (6; 2%), spleen (4; 1%) and others (26; 7%). A hormone hypersecretion syndrome was noted in 49 patients (24.1%), including the carcinoid syndrome (n = 37; 76%), Zollinger-Ellison syndrome (7; 14%), insulinoma syndrome (2; 4%), glucagonoma syndrome (2; 4%) and Verner-Morrison syndrome (1; 2%). Concurrent treatments which were performed during or immediately prior to nutritional status assessment were noted (table 2), as well as the current progression status of the tumour disease as reported by radiologic reports according to RECIST criteria [i.e. CR, partial remission (PR), stable disease (SD) and progressive disease (PD)].

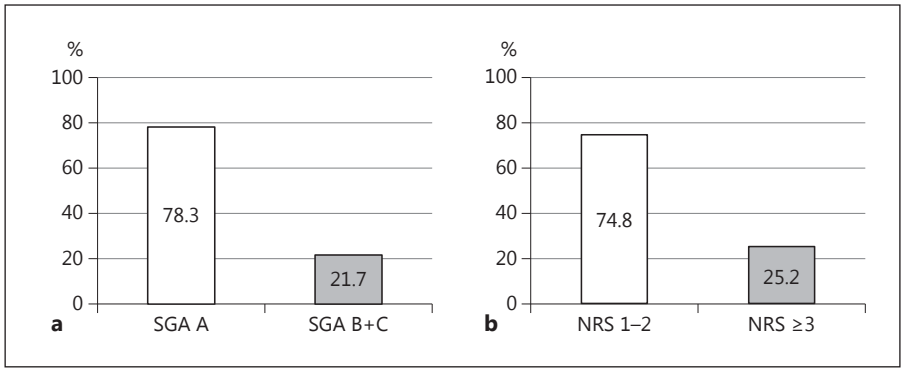

Fig. 1. Prevalence of malnutrition in NEN as assessed by SGA (**a**) or NRS (**b**).

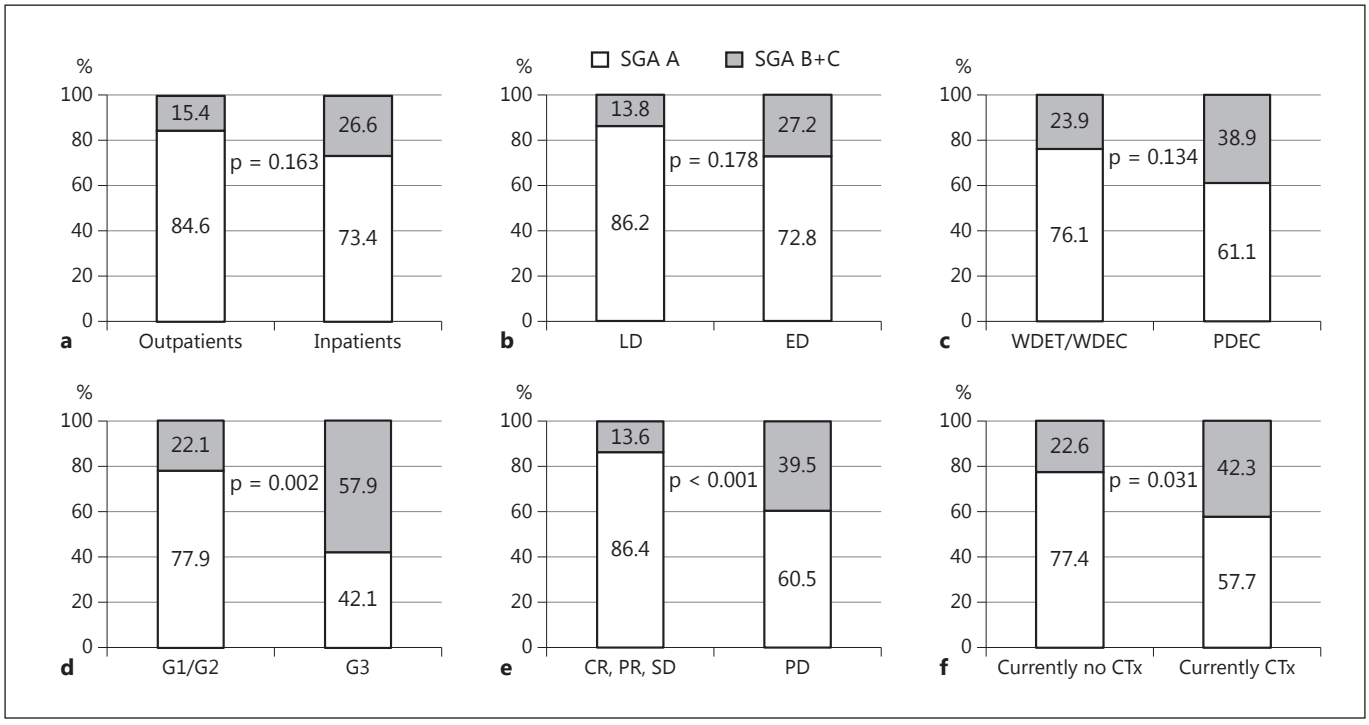

Fig. 2. Prevalence of malnutrition as defined by SGA (group A, i.e. no malnutrition, shown in white, and groups B, i.e. mild-to-moderate malnutrition, and C, i.e. severe malnutrition, together shown in grey) in subpopulations of NEN: outpatients versus inpatients (**a**), LD versus ED (**b**), WDET/C (WHO classification of 2000 according to Klöppel et al. [33]) versus PDEC (**c**), G1/2 NET versus G3 NEC (**d**), patients with initial diagnosis and CR/PR/SD versus patients with PD (**e**) and patients currently on no chemotherapy (CTx) versus patients currently on CTx (**f**).

Nutritional Status Assessment: Screening Scores

As shown in figure 1, nutritional status assessment performed by SGA and NRS resulted in the detection of malnourished patients (SGA groups B and C) or hospitalized patients at high risk of malnutrition (NRS scores ≥3) in 51 (25.1%) and 44 (21.7%) of the patients, respectively.

When analysing the prevalence of malnutrition in tumour-specific subgroups such as inpatients versus outpatients, patients with the limited tumour stages I–IIIA (LD) versus those with extensive metastatic tumour stages IIIB–IV (ED), patients classified according to the WHO classification of 2000 [33] versus those classified according to NEN grading, patients in remission or with SD versus those with PD and, finally, patients undergoing chemotherapy versus those undergoing none, all subgroups representative of a more severe, advanced or active tumour disease showed a higher prevalence of mal-

Table 3. Gender-specific results of anthropometry (body weight, BMI, MUAC, TST) and serum surrogate parameters depending on the screening score subgroup

	Sex	SGA		NRS	
		A	B + C	0–2	≥3
Body weight, kg	male	82.9±15.5 (82.1)	72.0±14.7 (73.0)	83.0±15.4 (82.1)	70.6±14.2 (71.0)
	female	69.8±13.3 (68.5)	58.8±12.3 (57.0)	69.7±12.7 (68.5)	56.6±12.8 (55.0)
BMI	male	26.5±4.4 (25.8)	24.8±3.5 (24.6)	26.5±4.4 (26.0)	24.2±3.4 (24.3)
	female	25.6±4.4 (24.9)	22.2±4.6 (21.6)	25.5±4.2 (24.9)	21.7±5.0 (20.3)
MUAC, cm	male	31.0±4.0 (30.0)	26.3±7.7 (27.5)	31.1±4.0 (30.5)	25.9±7.4 (27.5)
	female	29.6±4.0 (29.0)	27.0±4.5 (27.0)	29.7±4.1 (29.0)	26.0±3.7 (26.0)
TST, mm	male	12.4±5.3 (11.3)	11.1±7.0 (11.6)	12.6±5.3 (11.8)	10.1±6.5 (7.0)
	female	20.9±7.1 (20.0)	17.3±6.2 (17.0)	21.1±6.9 (20.0)	16.0±5.9 (15.5)
Albumin, g/dl	male	4.3±0.3 (4.4)	3.7±0.6 (3.5)	4.3±0.3 (4.4)	3.7±0.6 (3.5)
	female	4.3±0.3 (4.4)	3.8±0.7 (3.9)	4.3±0.4 (4.4)	3.7±0.6 (3.8)
Transferrin, mg/dl	male	266±50 (259)	225±70 (220)	267±51 (257)	220±63 (227)
	female	265±46 (262)	241±88 (234)	265±47 (263)	236±92 (211)
NRI	male	105.5±5.6 (105.8)	93.0±10.4 (90.4)	105.5±5.5 (105.5)	92.2±10.4 (90.4)
	female	106.0±5.9 (107.0)	94.3±12.6 (95.6)	105.8±6.7 (107.0)	92.1±11.9 (92.2)

Values are means ± standard deviation (medians).

Table 4. Gender-specific results of BIA depending on the screening score subgroup

	Sex	SGA		NRS	
		A	B + C	1–2	≥3
Phase angle α, °	male	5.4±1.0 (5.4)	4.5±1.1 (4.6)	5.4±1.0 (5.4)	4.4±1.0 (4.6)
	female	5.1±0.8 (5.2)	4.0±1.1 (4.0)	5.1±0.9 (5.2)	3.9±0.9 (3.9)
ECM/BCM index	male	1.08±0.25 (1.02)	1.41±0.46 (1.26)	1.07±0.25 (1.02)	1.44±0.44 (1.26)
	female	1.14±0.22 (1.10)	1.70±0.78 (1.48)	1.19±0.40 (1.10)	1.69±0.70 (1.49)

Values are means ± standard deviation (medians).

nutrition by both SGA (fig. 2) and NRS (data not shown); the higher prevalence of malnutrition reached statistical significance for G3 NEC, patients with PD and patients currently undergoing chemotherapy (fig. 2d–f).

Nutritional Status Assessment: Objective Parameters

Parallel to assessment by screening scores, the patients' nutritional status was assessed by anthropometric measurement of body weight, BMI, MUAC and TST, which consistently demonstrated decreasing results with decreasing nutritional status (SGA B and C or NRS scores ≥3; table 3).

Furthermore, serum albumin, transferrin and NRI as a composite score were measured, and they also consistently showed a decrease in serum protein synthesis and of NRI with decreasing nutritional status (table 3). In addition, serum albumin as well serum transferrin concentrations were statistically highly significantly lower in SGA B and C, i.e. mildly or severely malnourished patients (fig. 3a, b; data for NRS not shown).

Body composition analysis by BIA also resulted in statistically highly significant differences between well-nourished (SGA A) and malnourished (SGA B and C) NEN patients, as reflected in a decreased phase angle α and an increased quotient of ECM to BCM (ECM/BCM index), indicating the loss of BCM and an increase in ECM (fig. 3b; data for NRS not shown). The exactly measured values are gender-specifically given in table 4.

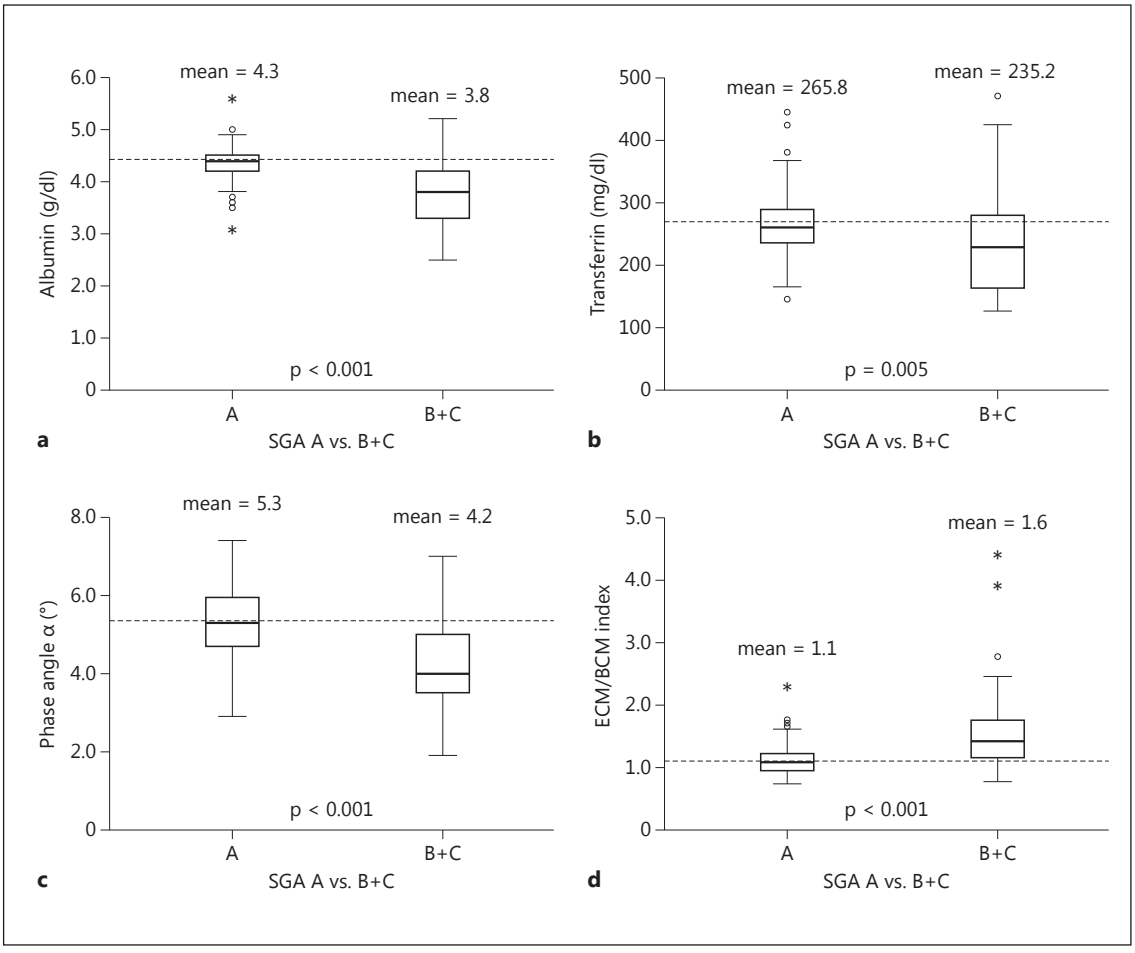

Fig. 3. Correlation of objective malnutrition parameters with nutritional status according to SGA. Serum surrogate parameters for malnutrition: albumin (**a**) and transferrin (**b**). BIA parameters: phase angle α (**c**) and ECM/BCM index (**d**).

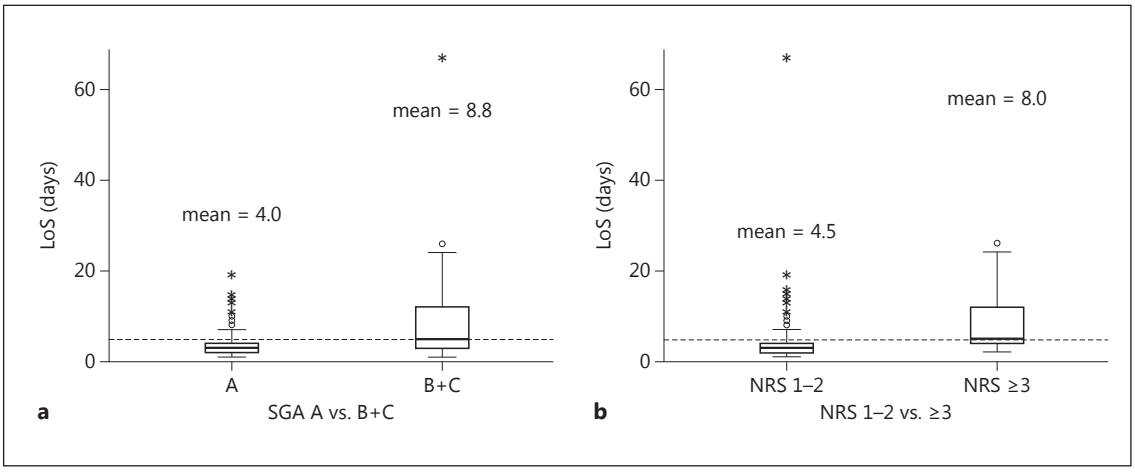

Fig. 4. Statistically significantly ($p < 0.001$) increased duration of hospitalizations (LoS) in association with malnutrition according to malnutrition scores. **a** SGA. **b** NRS.

Assessment of Clinical Outcome: LoS

As an immediate parameter of outcome, the LoS was assessed; it was demonstrated that inpatients with a poorer nutritional status (SGA B and C or NRS scores ≥3) required a statistically highly significant, longer stay in hospital ($p < 0.001$) before they were discharged (8.8 and 8.0 days vs. 4.0 and 4.5 days, respectively) as compared to patients with normal nutritional status (SGA A or NRS scores ≤2; fig. 4).

Assessment of Clinical Outcome: Survival Analysis

As a relevant clinical and oncological endpoint, overall survival was analysed and calculated from the time of nutritional status assessment (table 5; fig. 5). Mean overall survival was 28.9 months for the whole cohort, with a 1- and 2-year survival rate (YSR) of 90.3 and 80.7%, respectively (fig. 5a); median overall survival was not reached during the follow-up period of the study. When overall survival was analysed depending on the nutritional status as assessed by SGA (fig. 5b) or malnutrition risk as assessed by NRS (fig. 5c), overall survival turned out to be statistically highly significantly shorter in malnourished patients (SGA B and C) or patients at high risk of malnutrition (NRS scores ≥3), with correspondingly lower survival rates (table 5). This was paralleled by comparable results for patients with a poorer nutritional status as assessed by BIA (shown here is the standardized phase angle α according to Bosy-Westphal et al. [58]; fig. 5d).

To sort out potential confounders, the survival analyses according to nutritional status as assessed by SGA were also performed within subgroups of potential confounders (fig. 6). Even in the smaller, well-defined subgroups of WDET/C (fig. 6a), PDEC (fig. 6b) and G1/2 NET (fig. 6c), as well as in patients with advanced metastatic disease (ED; fig. 6d), in patients with PD (fig. 6e) and in patients undergoing chemotherapy (fig. 6f), a poorer nutritional status was associated with a significantly shorter long-term outcome and correspondingly lower survival rates (table 5).

Table 5. Outcome figures (mean OS, 1-YSR and 2-YSR) according to specific subgroups

	Mean OS, months	1-YSR, %	2-YSR, %	p value
Total	28.9	90.3	80.7	
SGA A	31.17	96.1	89.7	<0.001
SGA B + C	19.94	74.0	56.8	
NRS 1–2	30.69	94.8	87.4	<0.001
NRS ≥3	19.21	74.2	58.2	
α ≤5th percentile	30.70	94.7	87.7	<0.001
α >5th percentile	20.38	78.0	62.3	
WDET/C	29.76	93.8	83.3	<0.001
PDEC	15.61	52.9	52.9	
G1/G2	29.95	95.7	85.7	<0.001
G3	13.74	46.9	39.1	
LD	24.06	93.8	93.8	0.243
ED	28.55	89.6	79.2	
CR, PR, SD	31.03	97.2	90.7	0.004
PD	22.92	82.7	67.2	
Without CTx	29.61	92.5	83.8	0.037
On CTx	21.5	79.1	65.7	

OS = Overall survival; CTx = chemotherapy.

Table 6. Multivariate analysis of potential prognostic factors

Model 1				Model 2				Model 3			
included variables[a]	RR	95% CI	p value	included variables[b]	RR	95% CI	p value	included variables[c]	RR	95% CI	p value
Age	1.03	0.99–1.07	0.172	age	1.03	0.99–1.08	0.135	age	1.03	0.99–1.08	0.135
Sex	0.618	0.25–1.54	0.302	sex	0.49	0.19–1.26	0.139	sex	0.49	0.19–1.26	0.139
NRS ≥3*	1.75	1.06–2.89	0.028	SGA B + C*	5.34	1.78–15.96	0.003	α <5th percentile*	5.34	1.78–15.96	0.003
Stage IIIb–IV (ED)	3.94	0.44–35.56	0.222	stage IIIb–IV (ED)	3.34	0.37–29.91	0.280	stage IIIb–IV (ED)	3.34	0.37–29.91	0.280
G3*	6.95	2.17–22.23	0.001	G3*	5.54	1.71–17.90	0.004	G3*	5.54	1.71–17.90	0.004
PDEC	1.83	0.54–6.13	0.328	PDEC	2.60	0.74–9.16	0.138	PDEC	2.60	0.74–9.16	0.138
PD	1.91	0.64–5.69	0.243	PD	1.44	0.46–4.45	0.531	PD	1.44	0.46–4.45	0.531
Chemotherapy	1.31	0.51–3.40	0.574	chemotherapy	1.28	0.49–3.35	0.612	chemotherapy	1.28	0.49–3.35	0.612

RR = Risk ratio; CI = confidence interval. * Indicating statistical significance.

[a] Age, sex (male vs. female), NRS (NRS 0–2 vs. ≥3), stage [I–IIIa (LD) vs. IIIb–IV (ED)], ENETS Ki-67 grade (G1/2 vs. G3), WHO 2000 classification (WDET/C vs. PDEC), current growth behaviour (initial diagnosis + CR + PR + SD vs. PD) and current chemotherapy (yes vs. no).

[b] Age, sex (male vs. female), SGA (SGA A vs. B + C), stage [I–IIIa (LD) vs. IIIb–IV (ED)], ENETS Ki-67 grade (G1/2 vs. G3), WHO 2000 classification (WDET/C vs. PDEC), current growth behaviour (initial diagnosis + CR + PR + SD vs. PD) and current chemotherapy (yes vs. no).

[c] Age, sex (male vs. female), phase angle α (>5th vs. <5th percentile), stage [I–IIIa (LD) vs. IIIb–IV (ED)], ENETS Ki-67 grade (G1/2 vs. G3), WHO 2000 classification (WDET/C vs. PDEC), current growth behaviour (initial diagnosis + CR + PR + SD vs. PD) and current chemotherapy (yes vs. no).

Multivariate Risk Factor Analysis

To correct for confounding factors, an additional multivariate analysis was performed, comparing 3 models (table 6). Variables included in all models were age, gender, tumour stage (LD vs. ED), Ki-67 grade, WHO 2000 classification (WDET/C vs. PDEC), current growth behaviour (initial diagnosis, CR, PR and SD vs. PD) and current chemotherapy. Model 1 included malnutrition risk according to NRS, model 2 malnutrition according to SGA and model 3 the results of body composition measurement by BIA (i.e. the standardized phase angle α). As shown in table 6, only malnutrition and a high Ki-67 grade (G3 NEC) turned out to be statistically significant (NRS) or highly significant (SGA and phase angle α) independent risk factors for poorer outcome in the studied cohort. The relative risk of death was almost as high with poor nutritional status (SGA and phase angle α) as with a high proliferative index (risk ratio 5.34 vs. 5.54 for both risk factors). But even an increased risk of malnutrition, as indicated by an increased screening score with the NRS, resulted in a statistically significantly increased risk of death (1.75), proving the importance of nutritional status for the outcome of NEN patients.

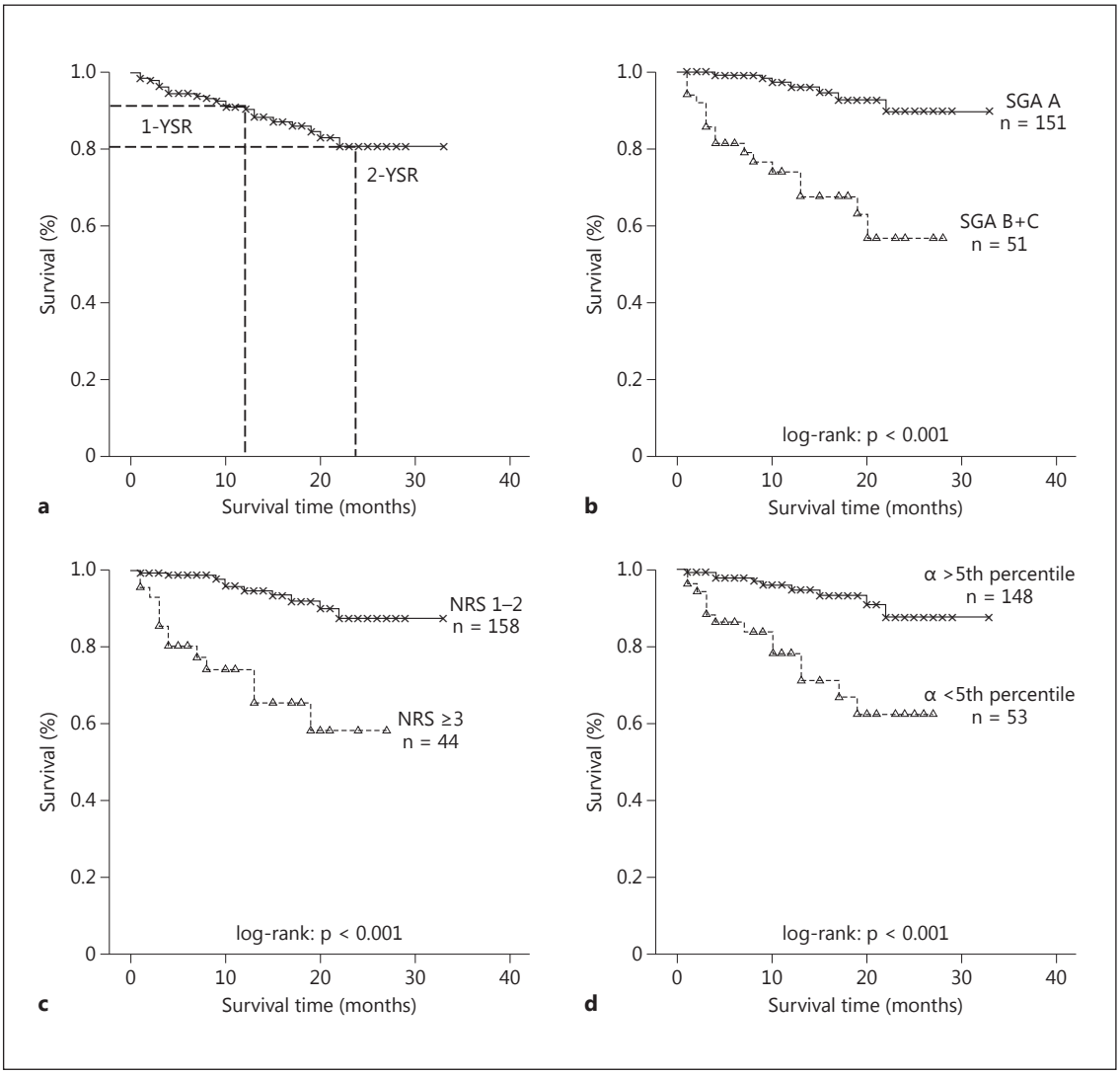

Fig. 5. Survival analysis of the complete cohort demonstrating overall survival of the whole cohort (**a**) and nutritional status-dependent overall survival according to SGA status (**b**), NRS status (**c**) and measurement of phase angle α by BIA (**d**).

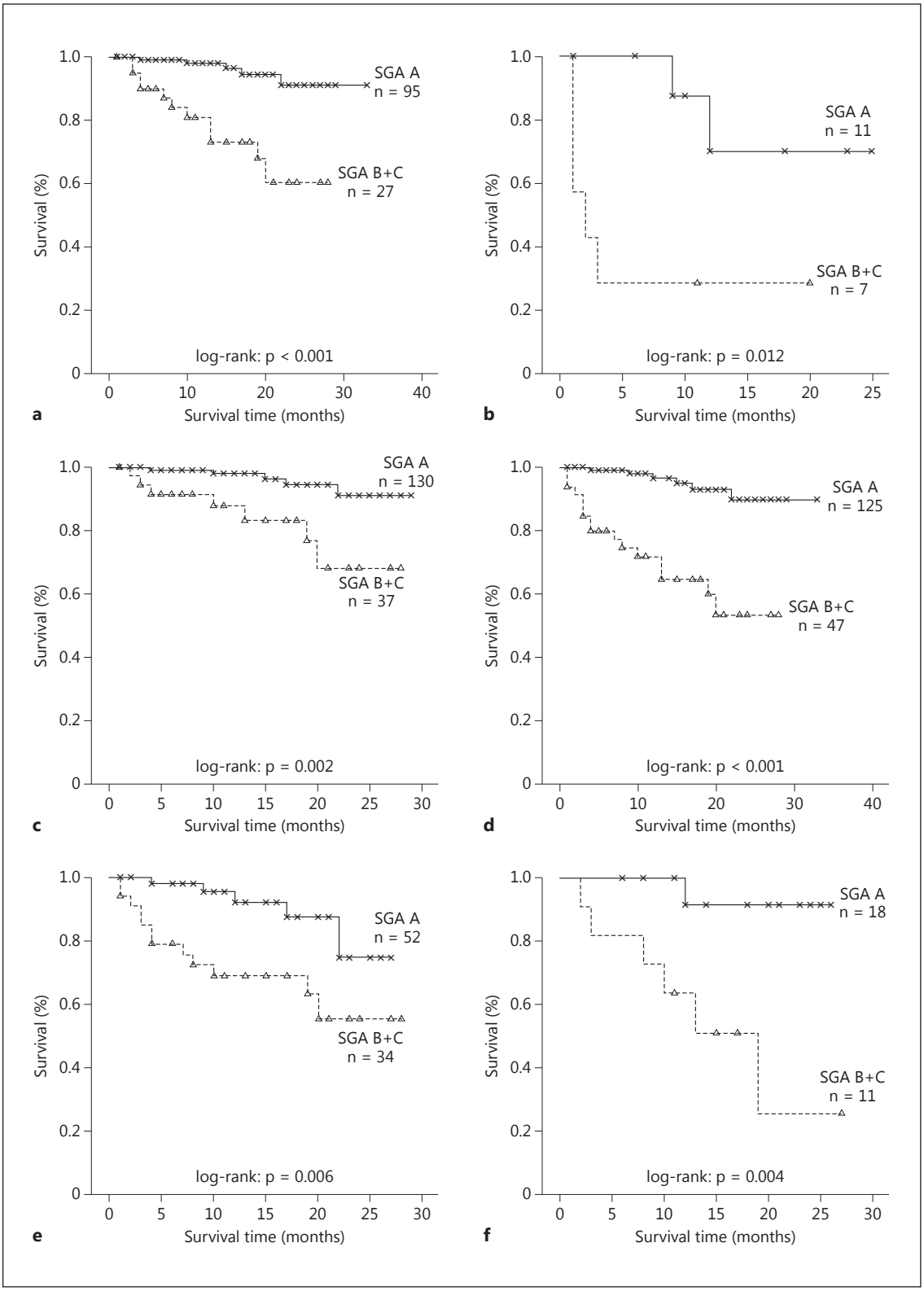

Fig. 6. Survival analysis for NEN-specific subgroups according to nutritional status as assessed by SGA: WDET/C (**a**), PDEC (**b**), G1/2 NET (**c**), stage IIIB/IV (ED; **d**), patients with PD (**e**) and patients receiving chemotherapy at the time of nutritional status assessment (**f**).

Discussion

In this cross-sectional study including a relatively long follow-up period, we could demonstrate for the first time that nutritional status is an important independent risk factor for poorer survival with NEN. Although NEN are a rather heterogeneous group of malignant neoplasms, we could show that nutritional status assessment – as has already been established for other solid malignancies – can reveal important subgroups of patients who have an increased risk of death due to poor nutritional status and thus probably need an appropriate diagnosis of malnutrition and adequate nutritional treatment in addition to their oncological therapy.

In this study, we detected malnutrition in 25.2% of the NEN patients by applying SGA and a risk of malnutrition in 21.7% of the NEN patients by using NRS (fig. 1). These figures for the prevalence of malnutrition with a malignant condition are relatively moderate when compared to other gastroenteropancreatic tumour entities such as oesophageal cancer (55–65%) [10], gastric cancer (30–45%) [10, 13, 14], pancreatic cancer (up to 70%) [15], colorectal cancer (40–60%) [14, 16, 17] or non-gastroenteropancreatic entities such as lung cancer (20–50%) [11, 12], breast cancer (20–30%) [16] or ovarian cancer (20–50%) [18–20]. This may be attributable to the fact that in the majority of cases NEN present as rather slowly growing neoplasms, presumably with a rather moderate 'cachexia-inducing' potential, which is also reflected in the rather good long-term prognosis, with 5- and 10-YSR of 40–60% in stage IV patients and even better figures in early-stage patients [28, 32, 36, 37, 62]. By assessing specific subgroups of NEN patients, we identified subgroups with a considerably higher prevalence of malnutrition; these were inpatients (fig. 2a), patients with a higher grade of malignancy (fig. 2b, c), patients with ED (fig. 2d) and patients with PD and undergoing chemotherapy at the time of the nutritional status assessment (fig. 2e, f). In some of these (fig. 2b, e, f), the observed difference was statistically significant even though the numbers of patients in each subgroup were rather limited. However, these differences between each subgroup appear to be plausible, because most of the mentioned criteria in fact reflect known risk factors for a more active tumour disease, a more rapid disease progression and ultimately a poorer outcome of NEN [32, 36, 37, 62]. It is thus important to identify such patients among the whole group of NEN patients, since malnutrition is much more prevalent in these patients (fig. 2), up to almost 40% in progressing patients and patients undergoing chemotherapy and even up to almost 60% in patients with G3 NEC with a high proliferative rate, a result comparable, for example, to that in advanced pancreatic cancer. Therefore, at least the above-mentioned NEN patient subgroups should be routinely checked for the presence of malnutrition in any oncological setting.

Several diagnostic tools are available for the diagnosis of malnutrition, and they have shown to be valid for NEN patients in this study comparably to patients with other solid neoplasms (tables 3, 4; fig. 3, 4). Screening scores have proven to be valid tools in many other solid neoplasms; particularly the SGA [46] has been shown to identify malnourished patients in malignant and non-malignant conditions reliably [5–7, 17, 20, 53, 54]. It is therefore not unexpected that the SGA also identifies moderately to severely malnourished NEN patients reliably, and that these results also correlate with anthropometric measurements and serum surrogate parameters (table 3; fig. 3a, b). However, for screening purposes, in routine clinical practice the SGA as well as anthropometric measurements beyond the BMI may be too complex and time-consuming, and serum surrogate parameters, while defining decreased hepatic protein synthesis due to protein-calorie malnutrition, may not be specific enough [5, 19, 50]. Thus, for screening purposes, the NRS has been established and proven to be a valid tool for identifying patients at high risk of malnutrition or actually malnourished [10, 43, 47, 52, 55, 56]. These NEN patients should then be further investigated with other methods. Accordingly, we have shown that NRS was able to detect roughly one quarter of NEN patients at risk of malnutrition, which was confirmed by the other nutritional assessment modalities (not all data are shown in this publication because of their comparability to the SGA results).

An important tool for defining a pathologically altered body composition, and potentially for monitoring further changes over time, is BIA [4, 12, 17, 54, 59]. In this study, it could also be demonstrated that malnutrition as defined by SGA and NRS was associated with significantly poorer BIA parameters (i.e. phase angle α and ECM/BCM index; table 4; fig. 3c, d). Similar changes have been observed with BIA analyses in other malignant diseases such as lung cancer [12], pancreatic cancer [15, 63], colorectal cancer [17] or breast cancer [64], with a particular focus on the direct measurement of phase angle α, as is also shown in this study. The direct measurement of BIA parameters, a widely available method among inpatient and outpatient nutrition teams, can thus provide an easily

measureable, reproducible and valid malnutrition indicator which will also allow monitoring of nutritional status during the disease and treatment course (including nutritional therapy). It is therefore a valuable and recommendable procedure for proving body compositional changes which occur together with malnutrition; it has thus also been recommended as a method for malnutrition assessment in several nutritional medicine guidelines [43, 65, 66].

Clinical outcome is an important tool for determining the consequences of changed nutritional parameters for a patient's further disease course. In this study, two parameters of clinical outcome were determined: LoS for inpatients and overall survival. As shown in figure 4, malnutrition (SGA B and C) or an increased risk of malnutrition (NRS scores ≥3) was associated with a significantly longer LoS. Similar observations within a comparable range of days have been made in other cancers or diseases [6, 7, 67], and they suggest that malnourished NEN patients with an increased LoS are likely to benefit from as little as a short-term nutritional intervention, and this may even be cost-effective in the current reimbursement systems (obviously depending on the respective health care system) [6].

While overall survival in the studied cohort was comparable to the general NEN survival rates [28, 32, 36, 37, 62], it is important to recognize that patients with a poorer nutritional status had a poorer outcome (fig. 5; table 5) irrespective of the method applied (SGA, NRS or BIA). Even more importantly, a detailed subgroup analysis (fig. 6) revealed statistically significantly poorer long-term outcomes in all the analysed subgroups, by this excluding some potential confounders. This means that malnutrition is an independent risk factor for poorer outcome in NEN, which was confirmed by multivariate analysis (table 6) testing for each of the methods applied to define malnutrition (SGA, NRS or BIA). In fact, malnutrition appeared to be an independent risk factor for death that was almost as powerful as a poor differentiation grade or a high proliferative index (G3), underlining the clinical importance of malnutrition for NEN patients' outcome, as has been shown for other cancers [68–70]. This has already been suggested by an analysis of the BMI in the context of hepatic transcatheter arterial chemoembolization in metastatic NEN patients [41] and in patients with pancreatic NEN receiving second-line or 'later-line' chemotherapy [34], a situation not identical to but resembling our analysis. However, to our knowledge, such a systematic workup of malnutrition criteria and risk factors for poor clinical outcome and its potential association with malnutrition had not yet been performed in NEN.

A possible limitation of this cross-sectional study is the fact that there is no simple and widely available gold standard for the assessment of malnutrition to which the results of our study could have been compared to. In fact, SGA was used as the internal standard of the study because it is a widely accepted scientific method for the assessment of nutritional status – which by itself is the result of multifactorial influences and thus difficult to be represented by a single method or parameter. Furthermore, disease-specific survival may in general, and in oncology in particular, better represent disease-specific risk factors, but this information is very difficult to obtain, particularly when patients reside far from specialized centres such as ours. However, in previous studies we have already demonstrated that approximately 67–75% of NEN patients ultimately die of their oncological disease and not of other causes [32, 35, 36], and therefore overall survival has proven to be an appropriate measure of long-term outcome also in NEN patients, particularly in those with advanced disease, recurrent disease or PD. Finally, although neither studied nor documented in our study protocol, some nutritional therapy was routinely provided to all malnourished patients (aside from all other oncological therapeutic interventions as listed in table 2), and therefore our outcome analysis cannot exclude effects derived from these interventions. It thus remains unclear whether overall survival can still be improved or whether it would have been worse without nutritional counselling and treatment. Future prospective comparative studies with structured nutritional interventions could approach this issue and should be performed to create a scientific basis for further nutritional treatments.

In conclusion, this study has demonstrated that malnutrition is a relevant clinical problem in NEN patients, with an impact on short- and long-term outcomes. By applying simple screening tools such as the NRS, which includes simple information such as the recent course of body weight, and further substantiating it using either widely available serum surrogate parameters of malnutrition (e.g. serum albumin levels) or measures of body composition such as BIA, a diagnosis of clinically meaningful malnutrition can be established. Based on our results, these procedures utilized for a proper diagnosis of malnutrition have a high sensitivity for the detection of malnutrition and can rather easily be integrated into clinical routine. Certainly, nutritional therapy should be initiated to improve a patient's clinical state and quality of

life and condition the patient for further treatments such as surgery, chemotherapy or some of the newly approved molecular targeted therapies which frequently are associated with some degree of weight loss [71–74]. The assumed beneficial effect of therapeutic nutritional interventions should be monitored not only via body weight, because this may be misleading in cases such as oedema formation, but also via the afore-mentioned serum surrogate parameters such as the course of serum albumin levels (taking into account the multiple differential diagnoses in the interpretation of the results) and via BIA measurements, which will likely represent the specific body compositional changes most precisely. Hereby, a patient's overall outcome, and presumably quality of life, will very likely be improved in a relevant fashion. However, the most appropriate approach to nutritional therapy should be studied to generate evidence for this obvious concept in order to improve supportive care for NEN patients.

Disclosure Statement

All authors declare to have no potential conflict of interest.

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