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Original article

Malnutrition predicts long-term survival in hospitalized patients with gastroenterological and hepatological diseases

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SUMMARY

Background & aims: Malnutrition is a common problem in hospitalized patients, influencing treatment outcomes, length of hospital stay, quality of life and overall survival. However, the association of nutritional status parameters with long-term mortality has not yet been studied systematically in gastroenterological-hepatological patients. The present study aimed to assess the association between nutritional status parameters as characterized by Nutritional Risk Screening (NRS), anthropometry, serum transferrin, bioelectrical impedance analysis (BIA) and long-term overall survival in hospitalized gastroenterological-hepatological patients.

Methods: Nutritional status was assessed in 644 gastroenterological-hepatological patients by NRS score. In addition, body mass index (BMI) and serum transferrin were determined and BIA was performed. Mid-upper arm circumference (MUAC) and triceps skinfold thickness (TST) were measured. Patients were followed for a mean period of 67 months (mean 54.8, range 0–107 months).

Results: During malnutrition screening, 475 (73.8%) patients were diagnosed as sufficiently nourished by NRS (NRS 0–2), while an increased risk of malnutrition was found in 169 (26.2%) patients (NRS≤3). Malnutrition was significantly associated with less favourable results for BMI ($p < 0.001$), serum transferrin ($p < 0.001$), BIA ($p < 0.001$), MUAC ($p < 0.001$) and TST ($p < 0.05$). Overall 5-year survival rates (YSR) were much shorter in malnourished patients whether with (5-YSR: 43.9%) or without (73.6%) malignancy. Overall 5-year survival rates (YSR) were much shorter in malnourished patients whether with (5-YSR: 43.9%) or without (73.6%) malignancy. By the multivariable analysis the NRS ≥3 and, phase angle (PhA) over the 5th percentile or over the mean of the cohort were found to be associated with long-term survival.

Conclusions: Malnutrition is highly prevalent in hospitalized gastroenterological-hepatological patients and is associated with distinct clinical diagnoses. In the present study we demonstrated that malnutrition characterized by the NRS, anthropometry, serum transferrin and BIA, not only predicts short-term but also significantly poor long-term outcome in these patients.

1. Introduction

Disease-related malnutrition is highly prevalent in hospitalized patients for both medical and surgical indications [1,2]. The association between malnutrition and higher in-hospital morbidity, short-term mortality, longer length of hospital stay and higher health care costs has been demonstrated in many clinical studies [3–9].

Abbreviations: BIA, Bioelectrical impedance analysis; BMI, Body mass index; CI, Confidence interval; FFM, Fat free mass; IBD, Inflammatory bowel disease; LoS, length of hospital stay; MUAC, Mid-upper arm circumference; NRS, Nutritional Risk Screening; OR, Odds ratios; PhA, Phase angle; X_c, Reactance; R, Resistance; SGA, Subjective Global Assessment; TST, Triceps skinfold thickness; UAMC, Upper arm muscle circumference; UAMA, Upper arm muscle area; (Y)SR, (Year) survival rates.

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Although there is no universally accepted definition of malnutrition, many nutritional assessment tools have been developed to obtain a reproducible measurement for an individual patient's nutritional status and to detect either an impeding risk for or an existing disease-related malnutrition. Currently, nutritional status assessment is based on various methods including clinical assessment tools, such as the Subjective Global Assessment (SGA) [10] or Nutritional Risk Screening (NRS) [11]. NRS has been demonstrated to identify patients at risk for disease-related malnutrition and includes the evaluation of nutritional status changes, disease severity and age of the patients [11–13]. SGA, considered the standard screening score [1,6,10,14–16] is a safe, inexpensive and effective clinical tool, completely based on clinical evaluations which is the reason for its "subjective" approach. It has been successfully used in a wide variety of patient populations [1,13,17–20]. It combines data from physical examination such as muscle mass, subcutaneous fat, manifest edema and/or ascites as well as aspects of medical history such as recent weight changes, gastrointestinal symptoms and changes in dietary intake.

In addition to such clinical scores anthropometric assessment is based not only on measurements of height and body weight but also on mid-upper arm circumference (MUAC), triceps skinfold thickness (TST) [21] and body composition [4,6,22]. Body composition can be assessed by bioelectrical impedance analysis (BIA), which is increasingly being used to assess nutritional status in patients with various diagnoses. BIA is a simple, non-invasive, reproducible and objective method, which measures resistance (R) - the relative contribution of fluid - and reactance (Xc) - the resistive effects produced by cellular membranes - by creating a voltage drop and afterwards phase shift in applied electrical current [22,23]. The phase shift is proportional to the ratio of reactance to resistance, also named phase angle (PhA). Current research has shown that higher values of the PhA are positively associated with cellular health and better cell integrity [24], while a lower phase angle is associated with cell death, decreased cell integrity [23] and an impaired nutritional status in severe diseases [25–32].

Furthermore, the serum transferrin as surrogates of protein turnover have been used to assess nutritional status in malignancies und benign diseases [33–36].

Here a prospective analysis of nutritional status-related long-term outcome in an initially cross-sectionally diagnosed and documented clinical in-patient cohort is presented. This study aimed to assess the predictive potential of malnutrition as characterized by NRS, anthropometry, serum surrogate parameters, and BIA, for all-cause long-term outcome as reflected by overall survival as ultimate patient-relevant outcome parameter in gastroenterological-hepatological patients.

2. Materials and methods

2.1. Patients

Between 2007 and 2010 nutritional status was routinely assessed in 644 consecutively patients admitted to the Department of Hepatology and Gastroenterology at Charité University Medicine Berlin, Germany, with a wide variety of gastroenterological-hepatological diagnoses. Patients were considered eligible for these examinations if they were 18 years or older, the intended hospital stay was longer than 24 h and they had consented to nutritional status investigations as part of clinical routine assessments for which informed consent had been obtained. Patients with defibrillators or implanted pacemakers as well as pregnant women were excluded because these clinical situations preclude the use of BIA.

2.2. Assessment of nutritional status

Measurements and questionnaires were performed by two nutritionists within 48 h after admission to the hospital. Patient-specific information such as date of birth, gender, height, body weight, weight changes, as well as main and secondary diagnoses was documented. Anthropometric measurements, laboratory parameters, and the results of BIA were recorded. Moreover, the length of hospital stay (LoS) at the time of nutritional status assessment was included. The time between the date of nutritional status examination and death or last patient contact was used for survival analysis. As major criterion for the classification of malnutrition NRS for malnutrition risk evaluation was used.

2.3. Nutritional Risk Screening

Nutritional status assessment by NRS was performed as previously described [11]. It is composed of nutrition status parameters (body mass index, percent recent weight loss and change in dietary intake), a severity score of the underlying disease and an adjustment for patients aged > 70 years. The maximum score amounts to 7 and patients with a total score of $\geq$3 were classified as "severely malnourished". Patients having a total score 0 or 1–2 were considered to have "absence of malnutrition" or "risk of malnutrition", respectively.

2.4. SGA questionnaire

The SGA questionnaire as established by Detsky et al. [37] incorporates patient's history regarding nutrition-related diseases, absolute body weight as well as weight losses during the last six months prior to assessment, changes in dietary intake, gastrointestinal symptoms, and anthropometric measurements (subcutaneous fat and muscle mass). Based on SGA questionnaire, each patient was classified as either well nourished (SGA A), moderately malnourished (SGA B) or severely malnourished (SGA C).

2.5. Anthropometric measurements

Body height was measured barefoot using a stadiometer (seca 220; seca, Hamburg, Germany) to the nearest of 0.5 cm. Actual body weight was measured with patients dressed using an electronic scale (seca 910; seca, Hamburg, Germany) to the nearest of 0.1 kg. The body mass index (BMI) was calculated as a relationship between weight (kg) and height (m) squared (kg/m^2).

TST and MUAC are two practical measurements for assessing nutritional status. The TST was measured to the nearest 0.1 mm with a Holtain calliper (Holtain Ltd., Crymych, UK). The MUAC was determined to the nearest of 0.1 cm in the middle between the olecranon and the acromion with a non-elastic tape on the non-dominant relaxed arm. UAMC and UAMA was calculated according to the formula by Gurney [38].

2.6. Blood parameters

Blood samples for serum transferrin were routinely drawn and determined at the time of the other investigations. Lower limit values for normal transferrin were $\geq$200 mg/dl as measured using immunoturbidimetry.

2.7. Bioelectrical impedance analysis

For the BIA measurements, we excluded patients with visible either hand of foot edema or both, patients with pacemakers as well as pregnant women.

Patients with ascites were not explicitly excluded [39] since BIA has been proposed to appropriately reflect body composition in cirrhotic patients with und without ascites [31,39]. BIA has also been applied successfully to patients with chronic severe diarrhoea and possible changes of the hydration status e.g. patients with short bowel syndrome [40,41] probably because these at least partially metabolically stabilized patients do not suffer from severe dehydration any more.

BIA measurements were performed using Nutriguard 2000-M device (Data Input GmbH, Darmstadt, Germany). Two pairs of current-introducing and voltage-sensing electrodes (Bianostic Classic, Data Input GmbH, Darmstadt, Germany) were placed at the back of the hand and foot of the dominant side of the body at predefined locations [22,42]. An alternating electric current of 800 μA at 5, 50 and 100 kHz was applied, and one assessment of resistance (R) and reactance (X_c) was made and documented. The phase angle (PhA) as the relation between the two vector components of impedance was calculated as previously described [43].

2.8. Statistical analysis

Statistical evaluation was performed using the SPSS 23.0 (SPSS inc, Chicago, IL). All continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test and further analysed using the t-test. Continuous values were given as median (min–max) for variables with a skewed distribution and as mean ± standard deviation for normally distributed variables. For ordinal scaled variables the Wilcoxon-Mann-Whitney test was applied. Categorical values were analysed using chi square test and Fisher's exact test and these variables were expressed as percentage or ratio.

Concordance between the two nutritional tools was tested by the *kappa* index of agreement. The results were interpreted as follows: no agreement <0; poor agreement 0–0.19; fair agreement 0.2–0.39; moderate agreement 0.4–0.59, substantial agreement 0.6–0.79, and almost perfect agreement 0.8–1.0 [44].

The analysis of overall survival was performed by using the Kaplan–Meier method and tested for significance using long-rank testing.

Total number of patients (“patients at risk”) included in the study was 644 pts (initially), 642 pts (1 year follow-up), 622 pts (2 years follow-up) and 263/8 pts (5/8 years follow-up) respectively.

For multi/univariable analysis of potentially independent predictors of mortality, three different Cox proportional-hazard models were explored. The first model included categorized PhA (below 5 th percentile) controlled for age and BMI, the second and the third model instead contained categorized NRS or PhA (mean of the cohort) resp. controlled for the same parameters. The results of the Cox regression analysis were given as hazard ratios (HR) and 95% confidence intervals (CI). A p value of <0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristic of patients

From November 2006 to August 2009, the nutritional status of 644 consecutively admitted gastroenterological and hepatological patients was acquired and documented. Table 1 summarizes the population characteristics. Almost equal gender distribution was encountered (female n = 291, male = 353). Mean age at initial evaluation of nutritional status was 58 years (median 60.5, range 18–95 years).

Table 1
Baseline characteristics in relation to main diagnosis in the study cohort.

	N (%)	Gender (m/f)	Age (years)	BMI (kg/m^2)
Benign GI-diseases	**447**	**242/205**	**54.6 ± 16.1**	**25.3 ± 5.6**
Liver cirrhosis	98 (21.9)	59/39	58.7 ± 11.8	25.5 ± 4.4
Pancreatitis	72 (16.1)	49/23	52.0 ± 13.5	25.1 ± 7.8
IBD	59 (13.0)	29/30	42.7 ± 16.2	24.2 ± 4.6
Biliary diseases	50 (11.2)	25/25	61.7 ± 15.2	24.3 ± 5.4
Polyp	17 (3.8)	9/8	62.8 ± 13.7	25.9 ± 3.7
GI-bleeding	43 (9.6)	23/20	64.5 ± 14.2	26.2 ± 5.6
Other benign diseases	108 (24.2)	48/60	55.0 ± 16.2	24.9 ± 5.9
Malignant GI-diseases	**197**	**110/87**	**65.0 ± 10.6**	**25.9 ± 4.8**
NEN	81 (41.1)	41/40	64.5 ± 11.9	26.4 ± 4.3
Stomach	8 (4.1)	4/4	61.9 ± 11.5	23.8 ± 5.4
Oesophagus	14 (7.1)	12/2	65.9 ± 8.7	26.4 ± 5.1
Liver	26 (13.2)	18/8	63.9 ± 8.2	26.2 ± 5.0
Pancreas	16 (8.1)	10/6	67.2 ± 10.5	27.9 ± 6.9
Biliary tract	13 (6.6)	9/4	64.9 ± 16.8	23.9 ± 2.8
Small/large intestine	24 (12.2)	13/11	67.5 ± 9.5	25.6 ± 5.1
Others malignancies	15 (7.6)	3/12	63.7 ± 10.5	23.1 ± 3.9
Total	**644 (100)**	**353/291**	**58.0 ± 15.4**	**25.4 ± 5.4**

GI = gastrointestinal; IBD = Inflammatory Bowel Disease, NEN = neuroendocrine neoplasia.

Table 2
Prevalence of malnutrition (scores ≥ 3) in the subgroups [n (%)].

	NRS groups		
	Group 0	Group 1-2	Group ≥3
Benign GI-diseases	23 (5.2)	319 (71.4)	105 (23.5)
Liver cirrhosis	1 (1.0)	70 (71.4)	27 (27.6)
Pancreatitis	0 (0.0)	49 (68.1)	23 (31.9)
IBD	1 (1.7)	43 (72.9)	15 (25.4)
Biliary disease	2 (4.0)	36 (72.0)	12 (24.0)
Polyps	4 (23.5)	12 (70.6)	1 (5.9)
GI-bleeding	4 (9.3)	34 (79.1)	5 (11.6)
Other benign diseases	11 (10.2)	75 (69.4)	22 (20.4)
Malignant GI-diseases	7 (3.6)	126 (64.0)	64 (32.5)
NEN	4 (4.9)	50 (61.7)	27 (33.3)
Stomach	1 (12.5)	4 (50.0)	3 (37.5)
Oesophagus	0 (0.0)	10 (71.4)	4 (28.6)
Liver	0 (0.0)	23 (88.5)	3 (11.5)
Pancreas	1 (6.3)	5 (31.3)	10 (62.7)
Biliary tract	0 (0.0)	8 (61.5)	5 (38.57)
Small-large intestine	1 (4.2)	17 (70.8)	6 (25.0)
Others malignancies	4 (9.3)	34 (79.1)	5 (11.6)
Total n = 644; 100%	**30 (4.7)**	**445 (69.1)**	**169 (26.2)**

GI = gastrointestinal; IBD = Inflammatory Bowel Disease; NEN = Neuroendocrine neoplasia.

3.2. Nutritional status assessment: screening scores

Nutritional status assessment was performed by the NRS resulted in detection of patients with a substantial risk of malnutrition and an indication for nutritional support (NRS ≥ 3).

Table 2 lists the prevalence of malnutrition among subgroups with different clinical diagnoses. NRS revealed an increased risk for malnutrition in 69.1% (NRS 1–2) and a significant malnutrition in 26.2% (NRS ≥ 3) of all patients. When analysing the prevalence of malnutrition in patients with the benign diseases, the risk of malnutrition was most prevalent in patients with *pancreatitis* (NRS ≥ 3: 31.9%), *liver cirrhosis* (NRS ≥ 3: 27.6%) and *inflammatory bowel disease IBD* (NRS ≥ 3: 24.0%). Similar results were also shown for SGA (Supplemental Table 1).

Table 2 displays the prevalence of malnutrition among subgroups with benign and malignant diseases.

In cancer patients malnutrition was most prevalent in patients with *pancreas cancer* (62.7%), *biliary tree cancer* (38.6%), *stomach cancer* (37.5%) and *neuroendocrine neoplasia* (33.3%).

Table 3
Mean values of studied malnutrition parameters according to diagnosis (malignant vs. benign).

	Benign	Malignant	P value
Age [years]	54.9 ± 16.1	65.2 ± 10.6	<0.001
BMI [kg/m^2]	25.3 ± 5.6	25.9 ± 4.8	0.646
TST [mm]	13.7 ± 6.7	15.7 ± 7.5	0.025
MUAC [cm]	28.5 ± 4.6	29.9 ± 4.9	0.009
Transferrin [mg/dl]	219.9 ± 76.1	241.4 ± 68.7	0.012
PhA [Grad]	4.9 ± 1.2	4.75 ± 1.2	0.145
Total (n = 644)	**447**	**197**	

BMI = body mass index; TST = triceps skinfold thickness; MUAC = mid-upper arm circumference; PhA = phase angle.

3.3. Criterion validity: objective parameters

Results of clinical score-based malnutrition assessment were substantiated by evaluation of anthropometric measurements, serum surrogate parameters of nutritional status (i.e. serum transferrin) as well as BIA results (i.e. PhA) as summarized in Table 3.

As shown in Table 4 mean values of anthropometric parameters such as body weight, BMI, TST and MUAC were significantly lower in patients classified as malnourished by NRS (NRS ≥ 3) as compared to those classified as well-nourished (NRS 0–1). Comparable results were seen for SGA (Supplemental Table 2).

Moreover, serum transferrin also consistently showed a decrease in serum protein synthesis with impaired nutritional status according to different nutritional screenings e.g. NRS (Table 4, Fig. 1, Supplemental Fig. 1 for another nutritional screening: SGA). The mean values of these serum protein concentrations were statistically significantly lower when compared to well-nourished patients.

As shown in Fig. 2, patients classified as malnourished had significantly lower mean phase angle, when compared with the well-nourished group.

3.4. Anthropometric characteristic

The anthropometric features of the cohorts with gender subgroups are shown in Table 5.

We also compared the TST, the UAC, the UAMC as well as UAMA to published percentiles of the normal population [21] (Table 5).

Figure 3 shows the correlation between NRS and the anthropometry (ROC curve). According to NRS results anthropometry of whole cohort demonstrated substantial predictive power for malnutrition; the TST [AUC: 0.727; CI: 0.67–0.79], the MUAC [0.650; CI: 0.58–0.71], the UAMC [0.679; CI: 0.62–0.74] and the UAMA [0.679; CI: 0.62–0.74].

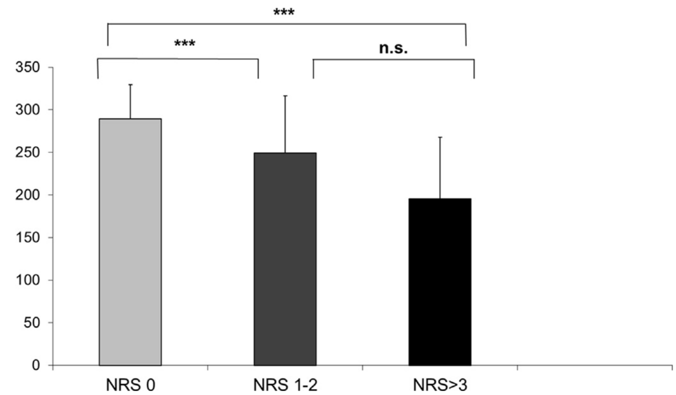

Fig. 1. Association between nutritional status and serum transferrin [mg/dl], ***p ≤ 0.001, n.s.: not significant.

3.5. Short-term outcome: length of hospital stay

As an indicator of short-term outcome, we analysed the impact of increased nutritional risk/malnutrition on the length of hospital stay (LoS) (Table 6). Patients without nutritional risk had a significantly ($p < 0.001$) shorter mean LoS of 4.1 days as compared to patients at nutritional risk as defined by various nutritional screenings e.g. NRS, who had a prolonged LoS of 10.0 days (NRS ≥ 3). Similar results were also shown for another nutritional screening: SGA (Supplemental Table 6).

3.6. Long-term outcome: overall survival

As a long-term clinical endpoint, overall survival was calculated. The median follow-up period was 67.0 months (range 0–107 months). The survival rate after 107 months was 62.4% (242

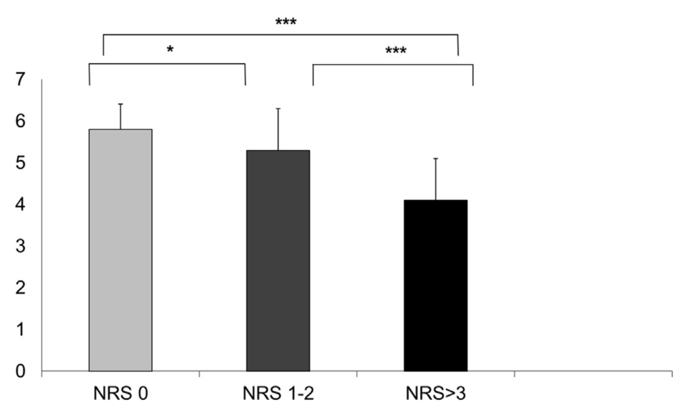

Fig. 2. Association between nutritional status and phase angle [°]. *p < 0.05, **p < 0.005, ***p ≤ 0.001, n.s.: not significant.

Table 4
Mean values of malnutrition parameters according to NRS groups (values are means ± standard deviation).

	Total	NRS			Significance		
		0	1–2	≥3	0 vs 1 + 2	0 vs 3	1 + 2 vs 3
BMI [kg/m^2]	644	27.3 ± 4.8	26.4 ± 5.2	22.8 ± 5.0	n.s	***	***
TST [mm]	322	19.8 ± 6.5	15.3 ± 7.2	12.3 ± 6.4	n.s	**	***
MUAC [cm]	324	34.0 ± 4.4	29.9 ± 4.5	26.6 ± 4.4	*	***	***
Transferrin [mg/dl]	292	289.4 ± 40.2	249.18 ± 67.4	195.5 ± 72.2	*	***	***
Weight change [kg]	644	+0.74	- 0.30	- 8.16	*	***	***
PhA [Grad]	393	5.8 ± 0.6	5.3 ± 1.0	4.1 ± 1.1	*	***	***
Total (n = 644)	**644**	**30**	**445**	**169**			

BMI = body mass index; TST = triceps skinfold thickness; MUAC = mid-upper arm circumference; PhA = phase angle; levels of statistical significance: *p < 0.05, **p < 0.005, ***p ≤ 0.001, n.s.: not significant.

Table 5
Anthropometric characteristic of the whole cohort and gender subgroups.

	TST	MUAC	UAMC	UAMA
Men				
Mean	12 ± 6	298 ± 45	260 ± 36	54.9 ± 16
Median	11 (2.4–39)	295 (200–500)	256 (183–408)	52 (27-13)
Below 5 th Percentile*	165 (11; 6%)	173 (23; 13%)	159 (10; 16%)	159 (10; 16%)
Women				
Mean	17 ± 7	227 ± 43	223 ± 30	40.4 ± 11
Median	16 (5–36)	275 (190–390)	221 (163–311)	29 (11–77)
Below 5 th Percentile*	144 (36; 25%)	149 (23; 20%)	131 (13; 10%)	131 (13; 10%)
Significance ANOVA gender	>0.00	>0.00	>0.00	>0.00.

TST Triceps Skinfold Thickness in mm; MUAC Upper arm circumference in mm^2; UAMC Upper arm muscle circumference in mm^2; UAMA Upper arm muscle area in cm^2.

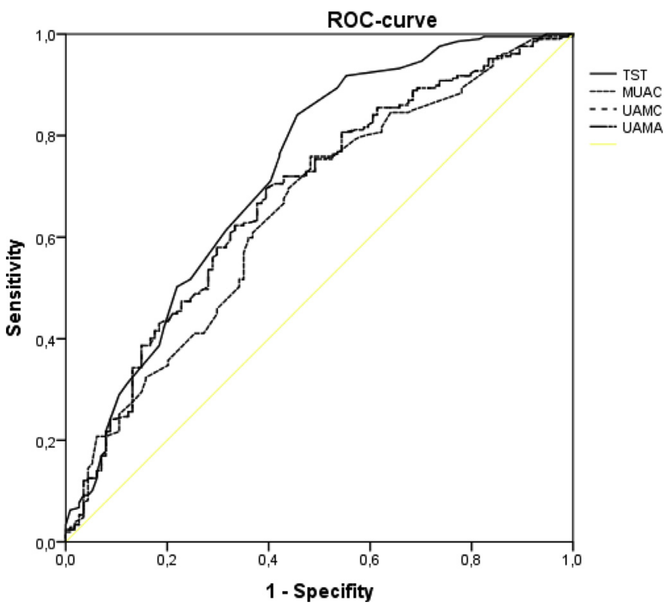

Fig. 3. ROC curve for the anthropometric measurements of the cohort: TST (n = 322, solid line), MUAC (n = 321, dotted line), UAMC (n = 321, dotted line short), UAMA (n = 321, dotted line long). Log-rank: p < 0.00 for all. TST = Triceps Skinfold Thickness in mm; MUAC = Mid-upper arm circumference in mm^2; UAMC = Upper arm muscle circumference in mm^2; UAMA = Upper arm muscle area in cm^2.

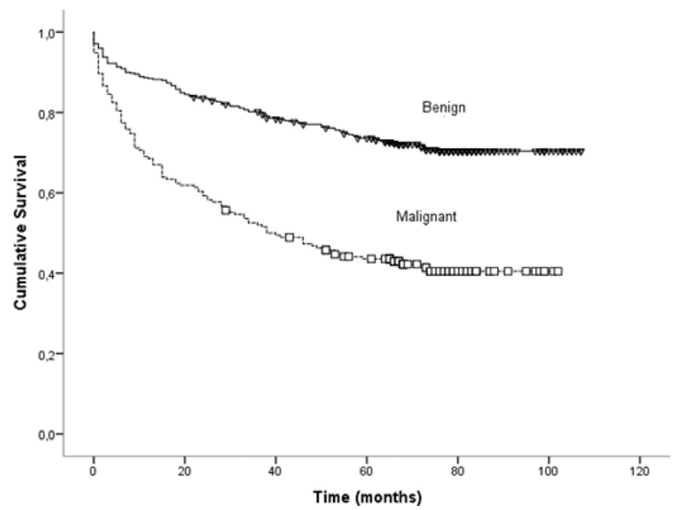

Fig. 4. Survival analysis of whole cohort demonstrating the overall survival of subgroups: benign (n = 450, solid line) and malignant (n = 194, dotted line). Log-rank: p < 0.001.

patients) for the whole cohort (with a 1-, 2-, 5- and 8 – year survival rate (YSR) of 82.8, 76.6, 64.5 and 61.5%, respectively (Supplemental Fig. 2). The survival rates were significantly related to the diagnosis (Fig. 1), particularly presence of an underlying benign (5-YSR 73.6% and 8 -YSR 70.4%) or malignant disease (5-YSR 43.9% and 8 -YSR 40.9%; p < 0.001) (Fig. 4).

Therefore, we separately analysed subgroups with and without malignancies for the influence of nutritional status parameters on the all-cause mortality (Figs. 5, 6).

Kaplan–Meier survival analysis showed that patients without malnutrition as defined by the “below the 5 th percentile of PhA” (Figs. 5a and 6a), by NRS (Figs. 5b and 6b), or by PhA (Figs. 5c and 6c) at baseline, were associated with a significantly higher (p < 0.001) survival rate in both groups with and without malignancies. PhA-results for benign and malignant subgroups were given separately, and grouped as above or below of the 5 th percentile or according or as cut off according to the respective mean PhA of 4.9° for benign diseases and 4.75° for malignancies (Table 3).

Overall 5- and 8-year survival rates (YSR) were significantly shorter (p < 0.001 for all) in malnourished patients than in non-malnourished patients with benign disease causes (Fig. 5): 5 th percentile: 5-YSR 85.7% vs. 55.7%, 8-YSR 84.8% vs. 52.5%, NRS: 5-YSR 78.5% vs. 57.7%, 8-YSR 75.4% vs. 53.9% and PhA 4.9°: 5-YSR 88.6% vs. 57.3% and 8-YSR 87.3% vs. 55.1%, respectively. Similarly, 5- and 8-YSR were worse in malnourished cancer patients (Fig. 6):5 th percentile: 5-YSR 58.9% vs. 27.5%, 8 -YSR 56.8% vs. 24.5%, NRS: 5-YSR 56.8% vs. 22.4%, 8 -YSR 53.4% vs. 14.6% and PhA 4.75°: 5-YSR 56.2% vs. 30.3% and 8 -YSR 55.3% vs. 26.5%, respectively.

Table 6
Mean ± SD length of hospital stay (LoS) in well-nourished patients (scores 0 and 1–2) and malnourished patients (scores ≥ 3); ***p ≤ 0.001, n.s.: not significant; (values are means ± standard deviation).

	NRS groups		
	Group 0	Group 1-2	Group ≥3
LoS days	4.1 ± 2.0	6.9 ± 5.9	10.0 ± 8.7
Significance	0 vs. 3 ***	0 vs. 1 + 2***	1 + 2 vs. 3***

LoS = length of hospital stay.

3.7. Multivariable risk factor analysis

We further performed a multivariable analysis to adjust for confounding factors, comparing three Cox regression models. Table 7 displays the adjusted hazard ratios (HR) for all-cause mortality in these three Cox regression models including gender, BMI (in all models). Furthermore, model I included malnutrition according to “PhA below 5 th percentile”, model II malnutrition risk

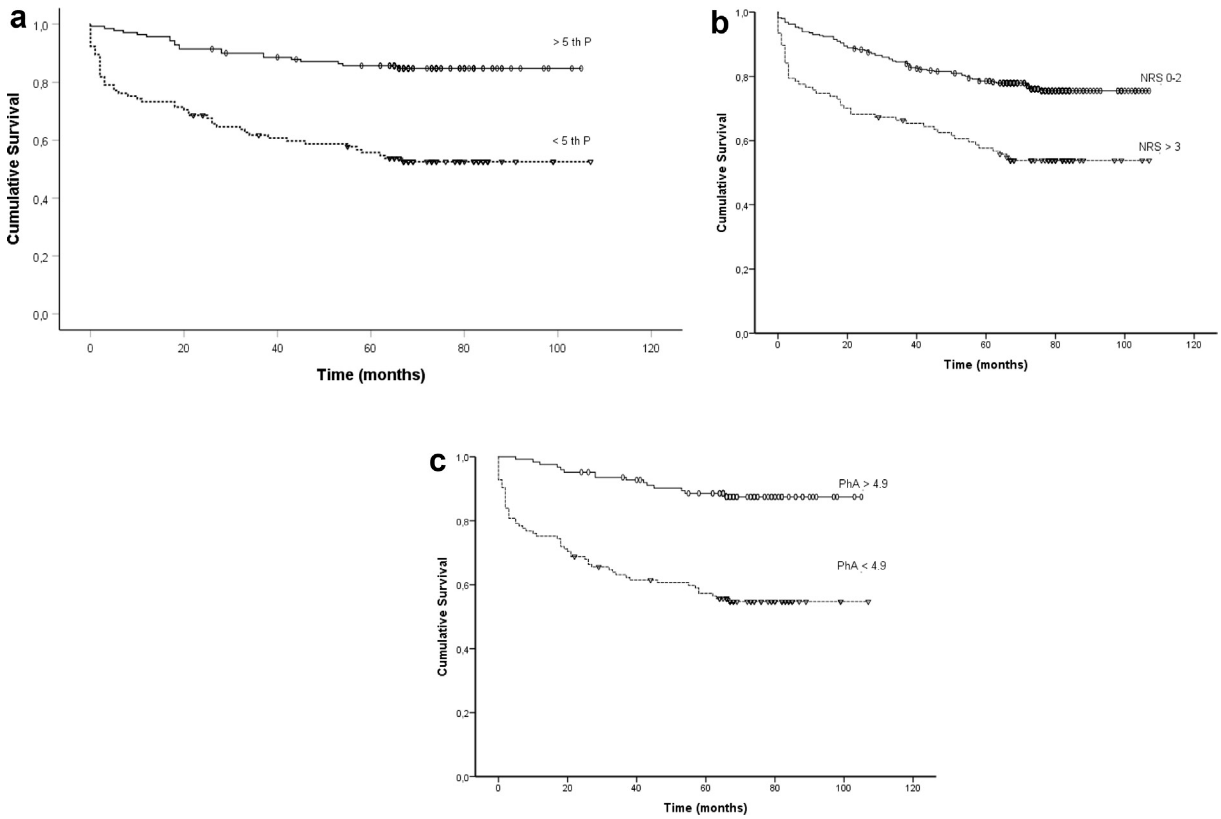

Fig. 5. Kaplan–Meier analysis of all-cause survival in the group with benign diseases (n = 450; measurement of phase angle in n = 246); nutritional status-dependent overall survival according to the 5 th percentile of PhA (a) and NRS status (b) and measurement of phase angle α (cut-off 4.9°) by BIA (c); well-nourished (solid line), malnourished (dotted line); Log-rank: $p < 0.001$ for all.

according to NRS, and model III the results of body composition measurement by BIA (cut off 4.9° as mean of PhA for benign diseases group and cut off 4.75° as mean of PhA for malignancies, respectively; Table 3).

As shown in Table 7 for patients with benign diseases, malnutrition or the risk of malnutrition (poorer quality of muscle mass were associated) with significantly higher relative risk of death.

In cancer patients risk of malnutrition and poorer quality of muscle mass had also statistically highly significant (Table 7) and independent impacts on long term mortality when compared to well-nourished patients.

4. Discussion

In this prospective both cross-sectional and longitudinal cohort study we demonstrate that malnutrition characterized by several independent methods such as, NRS, blood surrogate parameters and BIA is a strong independent predictor for poorer long-term overall survival in unselected but solely gastroenterogical and hepatological patients with and without underlying malignant disease. The major advantage of this study is the considerable sample size of the studied cohort as well as the length of follow up information. The risk of preterm death significantly increased in patients with malnutrition at baseline during long-term follow up. These data demonstrate that poor nutritional status is an important independent prognostic factor for hospitalized patients with gastroenterological and hepatological diagnoses. It also underlines the importance of assessing these patients and potentially intervening for improvement of this overall outcome predictor.

Malnutrition is highly prevalent in hospitalized patients with both gastroenteropancreatic as well as other underlying diseases and is associated with distinct clinical diagnoses. In accordance to other studies that report malnutrition rates between 20 and 65% [1,4,17,45,46], overall prevalence of malnutrition “a risk of malnutrition” in 25.7% patients by applying NRS in our investigation. By assessing specific subgroups classified according to either malignant or benign underlying diseases, the prevalence for malnutrition in malignancies ranged from 25% (small-large intestine) to 62.7% (pancreatic cancer). In concordance with others studies our results showed a similar prevalence in cancer patients. These ranged in the literature from 25% (neuroendocrine neoplasm) [34], 30–45% (gastric cancer) [5,47,48], 24–60% (colorectal cancer) [35,48–50], and up to 70% (pancreatic cancer) [6,29] with variation in results probably depending on used assessment methods for nutritional status.

Role of BMI was performed because it is still part of guidelines and common practise but proved by Cox-regression analysis to be of no specific value and thus not adding to diagnosing malnutrition.

Even though some studies have suggested that BMI may also be used in cirrhotic patients our data do not support this view. This may be because of the difficulty of applying standard BMI-cut offs to cirrhotic patients which leads to impractical diagnostic heterogeneity of cirrhotic patients, therefore BMI is of limited value for malnutrition assessment in cirrhotic patients and should thus be replaced by more valid assessments such as NRS.

By assessing specific subgroups with benign underlying diseases, the present study found a malnutrition prevalence between 6% (GI-polyps), 20% (biliary disease and GI-bleeding), 30% (pancreatitis) and 34% (liver cirrhosis and IBD, resp.). Currently available malnutrition studies demonstrated similar prevalence rates of malnourished patients regarding the main gastroenterological-hepatological diagnosis such IBD 487 (13–44%) [20,51,52],

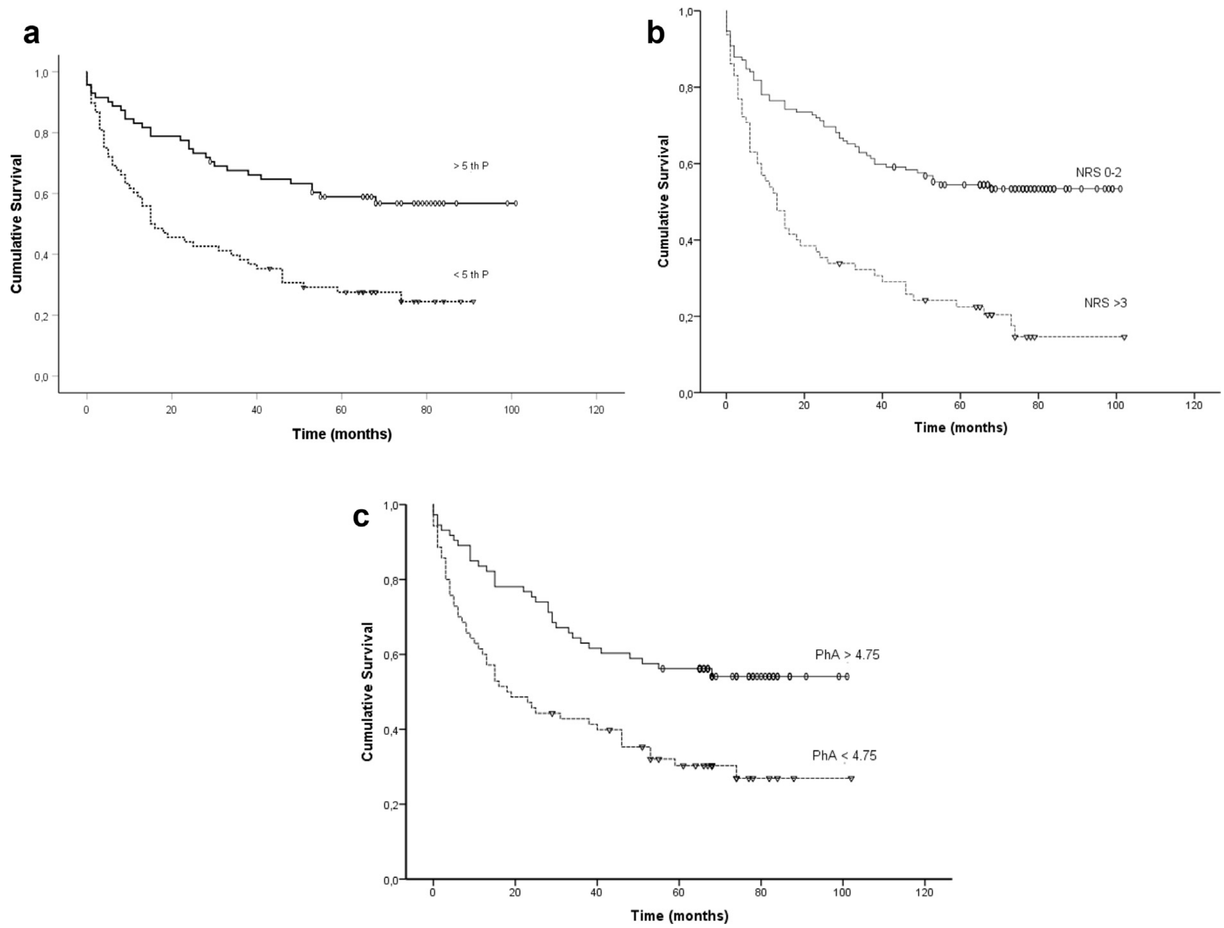

Fig. 6. Kaplan–Meier analysis of all-cause mortality in the group with malignant diseases (n = 194; by measurement of phase angle in n = 143); nutritional status-dependent overall survival according to the 5 th percentile of PhA (a) and NRS status (b) and measurement of phase angle α (cut-off 4.75°) by BIA (c); well-nourished (solid line), malnourished (dotted line); Log-rank: p < 0.001 for all.

pancreatitis (28–41%) [52,53], or liver cirrhosis (28–60%) [52,54–56] underlining the representativity of the studied cohort.

BIA is an important tool for the assessment of body composition and nutritional status [4,23,26,27,49,57] in both clinical routine as well as clinical science. BIA parameters, e.g. PhA, have been validated as reliable indicators of nutritional status and were reported to correlate with preterm mortality in various diagnosis groups such as patients with colorectal, breast, and lung cancer or gastroenterological benign diseases [25–31,58]. In this study, it could also be shown that the BIA parameters (i.e. PhA) are significantly lower in malnourished patients compared with the well-nourished group (Table 4) indicating the loss of functional cell mass, decreased associated outcome and thus a higher degree of disease severity [31,58]. Most importantly, NRS as well PhA were also strong independent predictors and may be more easily applied in clinical routine.

Finally and most importantly in the present study, two parameters of clinical outcome were studied: Length of hospital stay (LoS) as a short-term parameter as well as overall survival (OS) as long-term outcome parameter.

Patients with malnutrition in our study required a statistically highly significant, longer hospital stay (10 days vs. 5.5 days,

Table 7
Predictors of mortality according to benign or malignant disease cause by multivariate analyses of potential prognostic factors.

Models	N	Hazard Ratio (HR) 95% CI		Significance	
		benign	malignant	benign	malignant
I: Sex	644	1.25 (0.78–2.01)	1.64 (1.04–2.58)	0.357	0.035
BMI	644	1.02 (0.98–1.05)	0.96 (0.90–1.01)	0.336	0.100
PhA < 5 th	393	4.22 (2.50–7.14)	2.07 (1.26–3.42)	0.000	0.004
II: Sex	644	0.86 (0.52–1.44)	1.35 (0.90–1.92)	0.576	0.157
BMI	644	1.01 (0.98–1.05)	0.97 (0.93–1.02)	0.442	0.202
NRS >3	393	2.29 (1.32–3.96)	2.46 (1.65–3.65)	0.003	0.000
III: Sex	644	0.88 (0.62–1.26)	1.35 (0.97–1.86)	0.880	0.075
BMI	644	1.00 (0.98–1.03)	1.00 (0.98–1.03)	1.003	0.908
PhA < 4.9 or 4.75*	385	2.30 (1.48–3.58)	3.05 (2.17–4.29)	0.000	0.000

PhA <5 = PhA below 5 th percentile; BMI = body mass index; *PhA < 4.9 for benign diseases or PhA < 4.75 for malignancies.

respectively) as compared to well-nourished patients (Table 6). These results are in agreement with results from similar observations of hospitalized patients with gastroenterological diagnoses [1,2,59]. Thereby, increased malnutrition-related health-care costs are relevant to health care systems and there is strong evidence that treatment of malnutrition is economically beneficial at least for short-term outcome criteria [60,61].

In this study, we also demonstrated an association between malnutrition defined by NRS, BIA and long-term survival in gastroenterological-hepatological patients. Previous studies have investigated the association between malnutrition and long–term mortality among elderly [8,62–65], patients with parenteral nutrition [12], or patients with and without malignancies [13,48,66]. These publications have demonstrated that patients from these specific clinical groups with malnutrition have a poorer outcome. Our results support these results (Figs 5 and 6) irrespective of the applied method (NRS, BIA). Furthermore, this study to demonstrated the predictive potential of malnutrition defined by NRS and BIA and short as well as all-cause long-term outcome - with median follow up of more than 5 and up to 8 years - in gastroenterological-hepatological patients.

A possible limitation of this study is that due to the complexity of influences on nutritional status there is no simple, unequivocal and widely available standard for malnutrition assessment to date. Therefore, the NRS, which is a recommended tool by published guidelines [11,14,67], were used as internal references to estimate the prevalence of malnutrition. However, we cannot exclude the influence of other possible confounding factors such a disease severity (e.g. Child-Pugh score of cirrhosis, extent of ascites in chronic liver diseases, or pronounced diarrhoea), dietary habits or socioeconomic status, even though most parameters have been considered in this study. Finally, the results of the study were applied to a selected gastroenterological-hepatological patient group including respective malignancies, and cannot to be generalized to other in-patient populations. Moreover, potential neoplasia-specific outcome-confounders such as tumor stage, grade or current line and type of therapy as well as comorbidities were not analysed in this study setting and can therefore not be excluded as relevant influencers of long-term outcome of the subpopulation with malignant diseases within this study. However, a strong influence of malnutrition seems highly likely in these patients.

In summary, this study demonstrates the predictive potential role of a poor nutritional status in gastroenterological-hepatological patients as defined by the NRS and body composition parameters on both short-term and long-term outcome. Survival was highly significantly poorer in malnourished patients underlining the importance of the assessment of nutritional status in hospitalized patient and a potential long-term benefit of the respective patient with sufficient nutritional intervention.

5. Conclusion and clinical implications

This study shows, that disease-related malnutrition is associated with a high risk of reduced overall long-term survival in gastroenterological and hepatological inpatients with both benign and malignant diseases. Nutritional assessments as applied in this study can identify malnourished patients with high complementarity and reliably. These findings are clinically important and the results of our study supports further efforts to establish malnutrition screening programs and effective nutritional interventions against disease-related malnutrition particularly in hospitalized patients. Beyond this, further studies with structured nutritional interventions are needed to prove both clinical effectiveness and cost-effectiveness as well as individual safety of such interventions on long-term survival in gastroenterological and hepatological patients.

Conflict of interest

All authors declare to have no potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.02.010.

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