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Original article

Malnutrition is a prognostic factor in patients with hepatocellular carcinoma (HCC)

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SUMMARY

Background & aims: Malnutrition is a common, hence frequently underdiagnosed condition in patients with liver cirrhosis as well as in patients with cancer and has been shown to have a negative impact on survival in these patients. Frequently applied screening tools including anthropometric measurements or laboratory parameters to screen for malnutrition are not suitable for patients with liver cirrhosis with additional pathophysiological mechanisms leading to hypoalbuminemia and edema. Prospective data on the prevalence and prognostic impact of malnutrition in patients with HCC are scarce.
Methods: Fifty-one consecutive patients with hepatocellular carcinoma were prospectively enrolled into this study and screened for malnutrition by anthropometric measurements, the MNA score, the NRS score, laboratory work-up, and BIA measurement. The results of the different screening tools were compared to each other and with the BIA assessment and correlated with the outcome of patients.
Results: The calculation of a body mass index (BMI) was not suitable to identify malnourished patients with HCC. The MNA identified 19, the NRS score 17 patients at a risk for malnutrition. BIA revealed a reduction in relative body cell mass in 12 patients. Univariate Cox regression analyses identified tumor stage, MNA score, and phase angle obtained by BIA as significant factors with influence on survival. Multivariate analyses confirmed the phase angle at a cut-off of 4.8 to be an independent factor.
Conclusions: A significant proportion of patients with HCC is malnourished or at risk for malnutrition. Screening questionnaires and BIA measurement are superior to pure anthropometric measurements to identify the condition that negatively influences survival. The phase angle derived from body impedance analysis is an independent prognostic factor in patients with HCC.

1. Introduction

Malnutrition is a frequent, but underdiagnosed problem in cancer patients. It is defined as “decline in lean body mass with the potential for functional impairment” at multiple levels [1]. There is currently no single and universally accepted approach to the diagnosis and documentation of adult malnutrition [2], but it is estimated that about 32% of cancer patients are malnourished [3]. If a structured screening to detect malnutrition is not performed, more than half of the patients at risk for malnutrition in various settings are not recognized and are not referred for treatment [4].

Patients with hepatocellular carcinoma (HCC) are at a special increased risk for malnutrition. The liver is the central organ involved in the metabolism of nutrients, and in patients with liver cirrhosis malnutrition is a common attribute and associated with mortality and reduced quality of life [5]. In case of HCC, that in the majority of cases is associated with liver cirrhosis [6,7], tumor progression and tumor directed therapies can directly impact on liver function additionally [8].

Subjective global assessment (SGA) and anthropometric measurements are useful tools for the assessment of nutritional status in various diseases, but are not suitable for the precise assessment of nutritional status und do not correlate with outcome in patients

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with liver cirrhosis [9,10]. Ascites and hypoalbuminemia, frequent sequels of advanced liver cirrhosis, impede the application of the Body Mass Index (BMI) or the assessment of albumin as surrogate parameters for nutritional status.

Although several screening tools, amongst others questionnaires, have been developed to screen for malnutrition in cancer patients, a gold standard has not been defined yet and a screening is not performed on a routine basis in most outpatient departments.

The Nutritional Risk Score (NRS) [11] correlates with the clinical outcome of cancer patients in multivariate analyses [12]. A second questionnaire, the mini nutritional assessment (MNA) score, originally was designed for elderly patients at the age of 65 years or older. It also correlates independently with survival in patients with colorectal cancer and pulmonary cancer [13,14]. In patients with liver tumors the MNA score predicts the nutritional status accurately [15], but data on an impact on the clinical outcome of patients has not been published yet.

Bioelectrical impedance analysis (BIA) provides an additional option to obtain information on the nutritional status of patients, as malnutrition is associated with changes in the body composition. It is easy to use, non-invasive, reproducible and has been validated for the assessment of body composition and nutritional status in various patient populations, including cancer patients [16]. The phase angle reflects the relative contribution of fluid (resistance) and cellular membranes (capacitance) of the human body [17,18]. Results of BIA measurements correlate with prognosis in patients with HIV infection [19], chronic lung diseases including lung cancer [20–22], colon cancer [16], pancreatic cancer [17], and breast cancer [23]. Severe liver disease is characterized by significant reductions in body fat and body cell mass. In cirrhotic patients BIA therefore provides information on the cellular mass that is not significantly confounded by edema or ascites that may lead to false normal BMI or body weight [24]. Most Child A patients already present with a significant reduction in some nutritional compartments, and these changes occur in advance of physiological changes [25] and can only be detected by advanced assessment tools.

Data on screening of patients with HCC for malnutrition are scarce, and no data is published on the prognostic value of BIA measurements or other screening tools in these patients.

We therefore performed a prospective clinical study to evaluate the prevalence of malnutrition in patients with HCC, compared the results of different screening tools and analyzed the prognostic role of BIA assessments in these patients.

Table 1
Baseline characteristics of the cohort, $n = 51$.

Parameter		n (%)	Mean	SD
Gender	Male	44 (86.3)		
	Female	7 (13.7)		
Age (years)			66.18	9.82
	≤65 years	21 (41.2)		
	>65	30 (58.8)		
Liver cirrhosis	Yes	42 (82.4)		
	No	9 (17.6)		
Stage of liver cirrhosis	Not applicable	9 (17.6)		
	Child A	28 (54.9)		
	Child B	12 (23.5)		
	Child C	2 (3.9)		
Presence of ascites	Yes	14 (27.5)		
	No	37 (72.5)		
Hepatic encephalopathy	Yes	3 (5.9)		
	No	48 (94.1)		
Bilirubin (μmol/l)	$n = 47$		23.67	18.86
Albumin (g/l)	$n = 44$		35.61	6.34
Prothrombin time (%)	$n = 46$		92.91	21.57
ECOG status	0	36 (70.6)		
	1	9 (17.6)		
	2	4 (7.8)		
	3	2 (3.9)		
Number of HCC lesions	Unifocal	15 (29.4)		
	Multifocal	36 (70.6)		
Size of largest lesion			5.37	3.87
Infiltration of portal vein	Yes	12 (23.5)		
	No	38 (74.5)		
Presence of extrahepatic metastases	Yes	7 (13.7)		
	No	44 (86.3)		
BCLC stage	A	12 (23.5)		
	B	13 (25.5)		
	C	23 (45.1)		
	D	3 (5.9)		

2. Patients and methods

Fifty-one consecutive patients with hepatocellular carcinoma referred to the interdisciplinary HCC outpatient department of the University of Magdeburg were prospectively included into the study from January 1st 2013 to August 31st 2013 and followed-up until death. The database was closed on April 30th 2014. The study protocol was performed in accordance with current GCP guidelines and the declaration of Helsinki and approved by the local ethic committee of the University of Magdeburg. All patients gave their written informed consent to participate in the study.

The baseline characteristics of the patients are summarized in Table 1.

Demographic data (age, gender) and epidemiological characteristics including height, weight, calculated body mass index (BMI) and performance status at the time of examination were recorded. Survival time was defined as interval between the day of assessment and the date of death from any cause. If this information was not available or the patient was still alive the date was censored at the time of the last contact to the patient.

Liver cirrhosis was either diagnosed histologically or by typical clinical signs. Diagnosis of non-cirrhotic liver was based on reports of histopathological evaluation of liver tissue obtained by surgery at time of resection of HCC or obtained by biopsy from non-tumor tissue at time of diagnosis of HCC. In case of lacking histological confirmation, patients were classified as non-cirrhotic if they were completely free of any evidence of cirrhosis based on clinical, laboratory, and radiological findings.

Data on the cause of liver cirrhosis and stage according to Child-Pugh classification (concentrations of albumin and bilirubin in the serum, prothrombin time, and presence of ascites and/or hepatic encephalopathy) were extracted from the medical records.

Radiological reports were used for the assessment of tumor stage. Number and size of HCC nodules as well as the presence of distant metastases including lymph node involvement were recorded. If available, information on the patency of the portal vein was analyzed. The Barcelona-Clinic Liver Cancer (BCLC) stage was defined respecting tumor stage, liver function as assessed by Child-Pugh-score in patients with LC and clinical performance status of the patients.

All patients underwent anthropometric measurements (circumference of thigh and mid-upper arm circumference (MUAC)) and a BIA measurement with the assessment of a phase angle and computed analysis of derived parameters including quantification of extracellular water (ECW), intracellular water (ICW), total body water (TBW), fat mass (FM) and body cell mass (BCM) in addition to clinical and laboratory assessment. The measurement was performed using a BIACORPUS RX 4000 BIA analyzer (MEDICAL Healthcare GmbH, Karlsruhe, Germany). BIA was conducted while the patients were lying supine on a bed with their legs apart and their arms not touching the torso. All evaluations were conducted using the 4 surface standard electrode (tetra polar)