European Journal of Internal Medicine 104 (2022) 80–88

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Nutritional status in patients with hepatocellular carcinoma: Potential relevance for clinical outcome

Anne M. van Dijk [a], Bart J.P. Coppens [b], Maartje A. van Beers [c], Alexandra S. Bruins Slot [b], Carina J.R. Verstraete [b], Joep de Bruijne [b], Frank P. Vleggaar [b], Karel J. van Erpecum [b,*]

[a] Department of Internal Medicine and Dermatology, Dietetics, University Medical Center Utrecht, Utrecht, the Netherlands
[b] Department Gastroenterology and Hepatology, University Medical Center Utrecht, Heidelberglaan 100, Utrecht 3584 CX, the Netherlands
[c] Department of Head and Neck Surgical Oncology, Cancer Center, University Medical Center Utrecht, Utrecht, the Netherlands

ARTICLE INFO

Keywords:
Hepatocellular carcinoma
Nutritional status
Survival
Hand-grip strength

ABSTRACT

Background: Impaired nutritional status is a risk factor for unfavorable outcome in cirrhosis.
Methods: In this prospective cohort study in hepatocellular carcinoma patients referred for tumor-specific therapy, nutritional status was assessed before and 3 months post-treatment using 4 complementary tools: hand-grip strength (HGS), Liver Frailty Index (LFI), Patient-Generated Subjective Global Assessment (PG-SGA) and skeletal muscle index (L3-SMI). Uni- and multivariable analyses were performed using Kaplan Meier curves and Cox's regression analyses with correction for Barcelona Clinic Liver Cancer (BCLC) stage, alpha-fetoprotein and age.
Results: 56 patients were evaluated at baseline and 38 patients 3 months post-treatment. Baseline BCLC stage was 0 in 14%, A in 27%, B in 36%, C in 21%, and D in 2%. HGS, LFI, PG-SGA and L3-SMI were impaired in 13%, 95%, 21% and 71% respectively. Of all patients, 52% died after (median, range) 373 (32–962) days. Of the nutritional assessment tools, only HGS was independently associated with complication-free survival (HR 0.304, 95%CI 0.10–0.88: $p = 0.028$) and, approaching significance, with overall survival (HR 0.323, 95%CI 0.103–1.008: $p = 0.052$). Tumor-specific therapy was administered in 50 patients (20% radiofrequency / microwave ablation, 4% resection, 74% transarterial radio- or chemoembolization, 2% sorafenib). Three months post-treatment, complete response occurred in 44%, partial response in 20%, stable disease in 20% and progressive disease in 16%. Child-Pugh scores deteriorated and such deterioration was independently associated with reduced overall and complication-free survival.
Conclusions: reduced baseline HGS and deteriorated post-treatment Child-Pugh score are associated with reduced overall and complication-free survival in HCC.

1. Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related mortality worldwide [1]. Impaired nutritional status is a frequent phenomenon in patients with cirrhosis with clear negative impact on clinical course [2–7]. Impaired nutritional status also frequently occurs in cirrhotic HCC patients. Despite some negative studies [8,9], most available data suggest that impaired nutritional status is also associated with unfavorable outcome in patients with HCC in general [10–18] as well as after tumor-specific treatment, such as liver resection [19–22], radiofrequency ablation [23,24], sorafenib [25,26], Lenvatinib [27], embolization [28] or radiotherapy [29]. Many new therapeutic modalities have recently been introduced for HCC, but prognosis remains poor. Potential beneficial effects of early dietary interventions in these patient categories should be further explored if impaired nutritional status could be characterized in etiologic modeling studies as a risk factor causally related to unfavorable outcome.

Examples of nutrition disorders and nutrition related conditions [30] are sarcopenia (low muscle strength, low muscle quantity/quality and/or low physical performance) [31], frailty (impaired muscle contractile function that causes increased vulnerability and decreased physiologic reserve) [30] and malnutrition (imbalance of nutrient intake that causes adverse effects on patients' tissue, body form or function) [30]. Hand-grip strength (HGS) measured with a dynamometer reflects muscle strength [6]. CT-scan can be used to assess skeletal muscle mass [31]. Frailty can be assessed with the Liver Frailty Index (LFI) [32] and malnutrition with the Patient-Generated Subjective Global Assessment

* Corresponding author.
E-mail address: k.j.vanerpecum@umcutrecht.nl (K.J. van Erpecum).

https://doi.org/10.1016/j.ejim.2022.07.002
Received 24 February 2022; Received in revised form 21 June 2022; Accepted 5 July 2022
Available online 26 July 2022

AFP	alpha-fetoprotein
BCLC	Barcelona Clinic Liver Cancer
CFS	complication-free survival
CP	Child-Pugh
CT	computed tomography
EORTC-QLQ	European Organization for Research and Treatment for Cancer Quality of Life Questionnaire
HCC	hepatocellular carcinoma
HGS	hand-grip strength
L3-SMI	skeletal muscle index at 3rd lumbar vertebra
LFI	Liver Frailty Index
OS	overall survival
PFS	progression-free survival
PG-SGA	patient-generated subjective global assessment

(PG-SGA) [33].

In most previous studies in HCC patients, skeletal muscle mass was assessed by CT scan. Nevertheless, MRI-scan rather than CT-scan currently is the preferred radiological option to diagnose HCC. Also, CT-scan has a small risk of side effects, is expensive and evaluation of sarcopenia risk by CT-scan requires additional software. Therefore, other easy-to-use tools are necessary to detect nutritional risk in HCC patients.

The primary aim of this study was to explore the prevalence of reduced hand-grip strength, frailty, malnutrition and reduced skeletal muscle mass as well as their associations with overall survival (OS), complication-free survival (CFS) and progression-free survival (PFS) in HCC patients.

2. Patients and methods

2.1. Patients

In this prospective cohort study, all consenting patients with HCC who were referred to our tertiary center for tumor-specific therapy in the period September 2018 – April 2021 were included. The local Medical Ethical Committee had no objections to the study (research protocol 18/337) and all included patients provided written and signed informed consent. HCC was diagnosed according to European Association for the Study of the Liver Clinical Practice Guidelines [34]. Baseline evaluation comprised medical history including alcohol consumption ($\geq$3 daily consumptions in men and $\geq$2 daily consumptions in women were considered alcohol abuse), physical examination, laboratory tests, and magnetic resonance imaging (MRI-scan) of the liver and/or 3 phase CT-scan of the abdomen unless performed within one month from baseline. Body-mass index (BMI), World Health Organization Performance Status (PS), Child-Pugh (CP) score, Model for End-Stage Liver Disease (MELD) score, MELD-Na score and Barcelona Clinic Liver Cancer (BCLC) stage [34] were determined. Portal hypertension was defined as presence of either collaterals on radiological examination, esophageal varices by upper gastrointestinal endoscopy and/or thrombocytopenia. Quality of life was scored by the general European Organization for Research and Treatment for Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ C30) [35] and the liver cancer specific instrument (EORTC-QLQ HCC18) [36], in which global health status of EORTC-QLQ C30 and the summary score of EORTC-QLQ C30 and HCC18 [37] were used. Follow up occurred at least every three months, including laboratory and radiological examinations (generally MRI-scan).

2.2. Parameters of nutritional status

Baseline nutrition disorders and nutrition-related conditions were assessed in all consenting patients and repeated in all available cases

Table 1
Baseline patient and tumor characteristics.

Baseline table	Total (n = 56)
Age (years)	70 (43 – 86)
Male gender	50 (89)
Etiology	
HBV	2 (4)
HCV	7 (12)
NAFLD/NASH	17 (30)
Alcohol	20 (36)
Hemochromatosis	1 (2)
Other	2 (4)
Unknown	7 (12)
Cirrhotic[a]	48 (86)
Fibroscan[b]	
F0–2	2 (13)
F3–4	14 (87)
First treatment modality[c]	
Resection	2 (4)
RFA/MWA	10 (18)
TACE	12 (21)
TARE	25 (45)
Sorafenib	1 (2)
Best supportive care	6 (10)
Creatinine (μmol/L)	81 ± 24 (32 – 138)
Total bilirubin (μmol/L)	16 (4 – 98)
Alkaline phosphatase (U/L)	120 (46 – 416)
Gamma-GT (U/L)	156 (35 – 1080)
ASAT (U/L)	53 (16 – 590)
ALAT (U/L)	38 (11 – 228)
Albumin (g/L)	37 ± 5 (24 – 50)
Thrombocytes (x10^9/L)	135 (40 – 694)
PT-INR	1.22 (1.00 – 2.08)
Sodium (mmol/L)	138 ± 3 (130 – 144)
Alpha-fetoprotein (mcg/L)[d]	11 (2 – 170,000)
Portal hypertension	41 (73)
Varices	26 (46)
Collaterals	33 (59)
Thrombocytopenia	31 (55)
Ascites	
Absent	43 (77)
Slight	10 (18)
Moderate	3 (5)
Child-Pugh score	5 (5 – 10)
Child-Pugh class	
A (5–6)	46 (82)
B (7–9)	9 (16)
C (=/>10)	1 (2)
MELD-score	10 (6 – 24)
MELD-Na score	12 (7 – 24)
BCLC stage	
0	8 (14)
A	15 (27)
B	20 (36)
C	12 (21)
D	1 (2)
Performance score (ECOG)	
0	37 (66)
1	15 (27)
2	4 (7)
BMI (kg/m^2)	27 (20 – 46)
Weight (kg)	88 ± 17 (50 – 136)
ΔWeight in preceding month (kg)	0 (−33 – +9)
ΔWeight in preceding 6 months (kg)	−1 (−17 – +8)
PG-SGA total score	4 (1 – 14)
PG-SGA	
A well-nourished	44 (79)
B moderately malnourished	12 (21)
Liver frailty index score	3.99 ± 0.68 (2.46 – 6.33)
LFI diagnosis	
Robust	3 (5)
Prefrail	45 (81)
Frail	8 (14)
Handgrip strength	
Highest (kg)	34 ± 9 (16 – 52)
Reduced	7 (13)

(continued on next page)

Table 1 (*continued*)

Baseline table	Total ($n = 56$)
Chairtest[e]	
Time (s)	13 (7 – 29)
Impaired	9 (18)
CT-scan L3[f]	
Skeletal muscle index (cm^2/m^2)	46.4 ± 6.7 (31.1–65.0)
reduced skeletal muscle mass	30 (71)
EORTC-QLQ C30 Global health status	75 (33 – 100)
Summary score QoL (C30)	90 (49 – 100)
Summary score QoL (HCC18)	9 (0 – 48)
Duration of follow-up (days)	373 (32 – 962)

Data are presented as n (%), in case of parametric distribution as mean ± SD (range) or in case of nonparametric distribution as median (range).

[a] Based on clinical, radiologic or histologic data.

[b] Fibroscan was performed in 16/56 patients (29%).

[c] Four patients received additional second treatment more than three months after the primary treatment.

[d] available in 54/56 patients (96%).

[e] 6/56 patients (11%) were not able to perform or complete the chair test in less than 60 s and could not be included.

[f] CT-scan was available in 42/56 patients (75%).

three months post-treatment. Skeletal muscle mass was measured with the aid of Slice-O-Matic program as cross-sectional muscle area (SMA) at the third lumbar vertebra (L3) on CT. Muscle area was defined as the pixel area between the radiodensity range of −29 and + 150 Hounsfield Units (HU) which is specific for muscle tissue. The skeletal muscle index (SMI) was calculated by correcting SMA for height and expressed in cm^2/m^2. L3-SMI <39 cm^2/m^2 for women and <50 cm^2/m^2 for men were considered reduced SMI [38].

Hand-grip strength (HGS) was determined by squeezing an analog Jamar dynamometer three times with dominant hand and full-strength, having a neutral shoulder and forearm with the elbow at 90° The highest of three attempts below the 10th centile was taken to distinguish between reduced and normal HGS on age-bound, sex-specific cutoff values [39].

Frailty was determined with the Liver Frailty Index (LFI) [32]. Components of LFI are: **1.** HGS, **2.** five chair stands as fast as possible (one decimal accuracy and with a maximum of 60 s) and **3.** Balance testing in three different positions (side-by-side, semi-tandem, tandem: with a maximum of 10 s each). The LFI calculatorhttps://liverfrailtyindex.ucsf.edu/ was used to determine whether the patient was either robust, prefrail or frail.

Malnutrition was evaluated with the Patient-Generated Subjective Global Assessment (PG-SGA: version 3.7 NL, 2014) [33]. The PG-SGA consists of two components: the first part, regarding weight, nutritional intake, symptoms and functioning, was generated by the patient. The second part, about the patients' medical history, metabolic stress and physical examination, was completed by the healthcare professional. Patients were divided in three groups (*A* = well nourished, *B* = moderately malnourished or suspected malnutrition, C = severely malnourished).

2.3. Statistical analysis

IBM SPSS Statistics 26.0.0.1 was used to perform all statistical analyses. Categorical data are expressed as absolute numbers with percentage and compared with Fisher's exact test. Continuous variables are presented as mean ± SD (range) in case of normal distribution, or as median (range) in case of non-normal distribution. Independent samples t-tests or Mann-Whitney U tests were applied for comparison between two groups as appropriate. One-way ANOVA (with Tukey's HSD as post-hoc test) or Kruskal-Wallis tests (in case of non-normal distribution) were used for comparison of three groups. Differences in patient characteristics between baseline and three months post-treatment were evaluated the paired samples *t*-test or Wilcoxon signed-rank test as appropriate. A two-sided *p*-value < 0.05 was considered statistically significant.

Table 2
Relation between nutritional status and overall survival.

Overall survival ($n = 56$)	**Univariable analysis**		**Multivariable analysis[a]**	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**
L3-SMI[b]				
Reduced ($n = 30$)	Referent		Referent	
Normal ($n = 12$)	1.540 (0.673–3.523)	0.306	0.441 (0.121–1.610)	0.215
HGS baseline				
reduced ($n = 7$)	Referent		Referent	
normal ($n = 49$)	0.304 (0.121–0.762)	**0.011**	0.323 (0.103–1.008)	**0.052**
LFI stage baseline[c]				
Robust/prefrail ($n = 48$)	Referent		Referent	
Frail ($n = 8$)	0.946 (0.329–2.726)	0.919	3.017 (0.606–15.015)	0.177
PG-SGA stage baseline				
A ($n = 44$)	Referent		Referent	
B ($n = 12$)	1.416 (0.625–3.206)	0.404	1.038 (0.377–2.855)	0.942
ΔChild-Pugh score[d]		**0.003**		**0.003**
Deterioration ($n = 23$)	Referent		Referent	
Equal ($n = 18$)	0.233 (0.084–0.643)	0.005	0.210 (0.067–0.659)	0.008
Improvement ($n = 8$)	0.086 (0.011–0.661)	0.018	0.053 (0.006–0.455)	0.007
mRECIST at 3 monts[e]		0.077		0.641
Complete response ($n = 20$)	Referent		Referent	
Partial response ($n = 9$)	1.630 (0.458–5.794)	0.45	1.782 (0.363–8.753)	0.477
Stable disease ($n = 9$)	3.094 (0.912–10.501)	0.070	0.895 (0.139–5.760)	0.907
Progressive disease ($n = 7$)	4.413 (1.331–14.636)	0.015	1.922 (0.421–8.784)	0.399
ΔHGS[f]				
Deteriorated ($n = 3$)	Referent		Referent	
Equal ($n = 35$)	1.455 (0.192–11.046)	0.717	0342 (0.032–3.694)	0.377
ΔLFI stage[g]				
Deterioration ($n = 6$)	Referent		Referent	
Equal/ improvement ($n = 31$)	0.353 (0.109–1.142)	0.082	0.598 (0.105–3.417)	0.563
ΔPG-SGA stage[f]		0.383		0.614
Deterioration ($n = 8$)	Referent		Referent	
Equal ($n = 26$)	0.656 (0.201–2.141)	0.485	0.554 (0.152–2.011)	0.369
Improvement ($n = 4$)	1.616 (0.357–7.301)	0.533	0.966 (0.149–6.275)	0.971

[a] In multivariable analyses the following baseline confounding variables were included: BCLC stage, alpha-fetoprotein (<1000 mcg/L versus ≥1000 mcg/L) and age.

[b] CT scan was available in 42 patients.

[c] Robust and prefrail combined, since only 3 patients were robust.

[d] Child-Pugh score at 3 months post treatment available in 49 patients.

[e] mRECIST 3 months post-treatment available in 45 patients.

[f] HGS and PG-SGA at 3 months post-treatment available in 38 patients.

[g] LFI at 3 months post-treatment available in 37 patients.

Our primary aims were: **1.** to explore in HCC patients referred for tumor-specific treatment, the prevalence of reduced hand-grip strength, frailty, malnutrition and reduced skeletal muscle mass and **2.** to examine their associations with overall (OS), complication-free (CFS) and tumor-

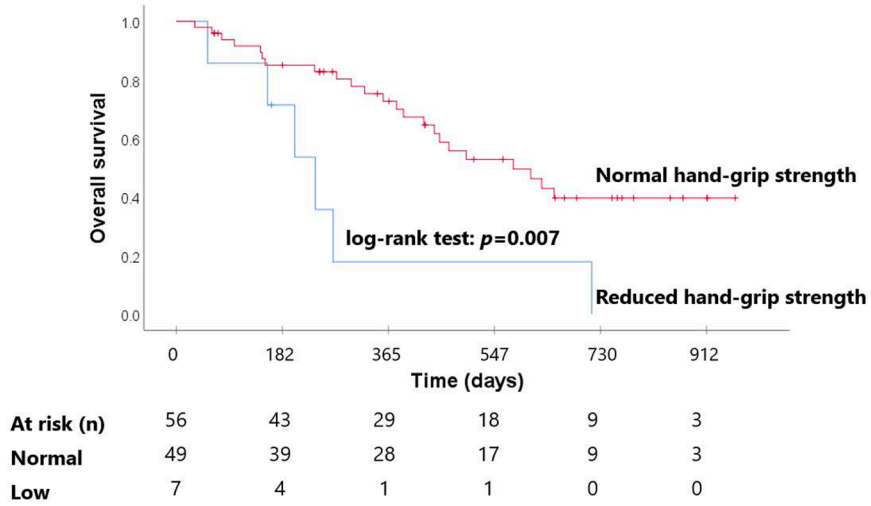


Fig. 1. Kaplan-Meier curve shows reduced overall survival in patients with reduced handgrip strength (log-rank test: $p = 0.007$).

progression free (PFS) survival. Secondary aims were: **1.** To compare nutritional status at baseline and at 3-months posttreatment and **2.** to evaluate whether at 3-months follow up, deteriorated nutritional status, deteriorated liver function (Child-Pugh score) or worse tumor response (based on modified response evaluation criteria in solid tumors (mRECIST [40]) were associated with reduced OS, CFS or PFS.

Follow-up ended at the final date of evaluation (1st of May 2021) or earlier in case of death from any cause (for OS, CFS), or first complication (for CFS), whatever came first. The following events were considered as complications: ascites, (bacterial) infection, variceal bleeding, hepatic encephalopathy, (severe) icterus, stroke, heart attack or death. PFS was evaluated for those patients who received tumor-targeting treatment and started at the date of measurement at baseline and ended at the date of first diagnosed recurrence or progression of the tumor or the first newly diagnosed metastasis after treatment, or at time of death from any cause whatever came first.

For the statistical analyses regarding our primary aims, patients were divided in subgoups, based on L3-SMI, HGS, frailty (LFI) or malnourishment (PG-SGA). Patients were divided in two groups for each parameter: reduced L3-SMI versus normal L3-SMI, reduced versus normal HGS, non-frail (i.e. robust and prefrail combined) versus frail for LFI and well-nourished (grade A) versus malnourished (grade B or C) for PG-SGA respectively. Then, the relation of the nutritional parameters (HGS, LFI and PG-SGA, L3-SMI) at baseline with OS, CFS and PFS was explored, using the Kaplan Meier method and univariable Cox's regression analyses. For our secondary aims a similar approach was used.

We wanted to explore whether our variables of interest could be a risk factor causally related to poor outcome, in light of potential therapeutic consequences. Therefore, according to the rules for etiological modeling studies [41,42], in the subsequent multivariable analyses, our variables of interest were corrected for the pre-defined variables BCLC stage, AFP and age based on the extensive pre-existing literature of the considerable impact of these three confounders on outcome in hepatocellular carcinoma.

3. Results

3.1. Baseline and tumor characteristics

Of all 86 patients with HCC initially referred for tumor-specific therapy in the study period, 56 patients could have a complete baseline assessment (flowchart Supplementary Fig. 1).

There were no significant differences in patient or tumor characteristics between these 56 patients and all 86 referred patients. Baseline characteristics of the included patients are given in Table 1.

Median age was 70 years and 89% of the patients were male. Cirrhosis was present in 86% of patients. Most frequent underlying causes of liver disease were alcohol abuse (36%), non-alcoholic steatohepatitis (30%) and hepatitis C (12%). Portal hypertension was present in 73%, as indicated by the presence of varices (46%), collaterals (59%) and/or thrombocytopenia (55%). Baseline BCLC stage was 0 in 14%, A in 27%, B in 36%, C in 21% and D in 2%. Child-Pugh class was A in 82%, B in 16% and C in 2%.

3.2. Baseline nutritional status

Detailed baseline nutritional characteristics are given in Supplementary Table 1.

L3-SMI (available in 42 cases) and HGS were reduced in 71% and 13% respectively. According to LFI, 5% of patients were robust, 81% prefrail and 14% frail. Frail and prefrail patients exhibited worse quality of life, according to EORTC-QLQ C30 Global Health Status and EORTC-QLQ C30 summary scores (Supplementary Table 1). According to PG-SGA, 79% of patients were well nourished (stage A) and 21% were moderately malnourished (stage B) at baseline. Quality of life according to EORTC-QLQ C30 Global Health Status and EORTC-QLQ HCC 18 summary score, was significantly worse in case of malnourished patients. In the 42 cases with all four nutritional parameters available, impaired nutritional status according to 0, 1, 2 or 3 parameters was found in 17%, 52%, 19%, and 12% respectively. Underlying cause of liver disease did not affect the nutritional parameters.

3.3. Overall survival: association with baseline parameters

During the study period, 52% of all patients died, after a median follow-up time of 373 days (range 32 – 962 days). OS was worse in case of higher Child-Pugh scores and higher BCLC stages (Supplementary Figs. 2 and 3). Concerning our confounding variables, in uni- and multivariable analyses, BCLC stage and age were independently associated with OS and AFP approached significance ($P = 0.07$). Concerning our main variables of interest, in univariable Cox-regression analysis, HGS was the only parameter of nutritional status significantly associated with OS (Table 2). Although patients with Child-Pugh class B or C often exhibited low HGS, there was significant overlap with Child-Pugh class A patients (Supplementary Fig. 4).

Kaplan Meier analysis for the effect of HGS on OS is shown in Fig. 1.

In multivariable Cox-regression analysis with correction for the

Table 3
Relation between nutritional status and complication-free survival.

Complication-free survival ($n = 56$)	Univariable analysis		Multivariable analysis[a]	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
L3-SMI baseline[b]				
reduced ($n = 30$)	Referent		Referent	
normal ($n = 12$)	1.870 (0.843–4.152)	0.124	1.099 (0.353–3.426)	0.870
HGS baseline				
reduced ($n = 7$)	Referent		Referent	
normal ($n = 49$)	0.286 (0.111–0.738)	**0.010**	0.304 (0.105–0.881)	**0.028**
LFI stage baseline[c]				
Robust/prefrail ($n = 48$)	Referent		Referent	
Frail ($n = 8$)	0.777 (0.272–2.217)	0.637	1.288 (0.307–5.401)	0.729
PG-SGA stage baseline				
A ($n = 44$)	Referent		Referent	
B ($n = 12$)	1.629 (0.751–3.536)	0.217	1.350 (0.547–3.332)	0.515
ΔChild-Pugh score[d]		**<0.001**		**0.002**
Deterioration ($n = 23$)	Referent		Referent	
Equal ($n = 18$)	0.176 (0.064–0.482)	0.001	0.179 (0.058–0.551)	0.003
Improvement ($n = 8$)	0.142 (0.032–0.627)	0.010	0.121 (0.024–0.601)	0.010
mRECIST[e]		0.530		0.956
Complete response ($n = 20$)	Referent		Referent	
Partial response ($n = 9$)	1.193 (0.366–3.891)	0.769	1.308 (0.316–5.417)	0.711
Stable disease ($n = 9$)	1.699 (0.559–5.161)	0.350	1.114 (0.238–5.201)	0.891
Progressive disease ($n = 7$)	2.171 (0.722–6.529)	0.167	1.415 (0.334–5.991)	0.637
ΔHGS[f]				
Deteriorated ($n = 3$)	Referent		Referent	
Equal ($n = 35$)	2.072 (0.275–15.581)	0.479	0.890 (0.098–8.075)	0.918
ΔLFI stage[g]				
Deterioration ($n = 6$)	Referent		Referent	
Equal/improvement ($n = 31$)	0.115 (0.037–0.359)	**<0.001**	0.081 (0.014–0.467)	**0.005**
ΔPG-SGA stage[f]		0.509		0.440
Deterioration ($n = 8$)	Referent		Referent	
Equal ($n = 26$)	0.708 (0.227–2.208)	0.552	0.434 (0.111–1.695)	0.230
Improvement ($n = 4$)	1.451 (0.324–6.498)	0.627	0.759 (0.123–4.684)	0.767

[a] In multivariable analyses the following confounding variables were included: baseline BCLC stage, alpha-fetoprotein (<1000 mcg/L versus ≥1000 mcg/L) and age.
[b] CT scan available in 42 patients.
[c] Robust and prefrail combined, since only 3 patients were robust.
[d] Child-Pugh score at 3 months post treatment available in 49 patients.
[e] mRECIST at 3 months post-treatment available in 45 patients.
[f] HGS and PG-SGA at 3 months post-treatment available in 38 patients.
[g] LFI at baseline and 3 months post treatment available in 37 patients.

confounders BCLC stage, AFP and age, this association was on the border of significance (HR 0.323 (0.103–1.008: $p = 0.052$: Table 2).

3.4. Complication-free survival: association with baseline parameters

Complications occurred in 32 patients (57%). Median CFS time was 225 (range 7 – 962) days. Complications included infection (31%: 3 pneumonia, 2 erysipelas, 1 pyelonephritis, 1 spontaneous bacterial peritonitis, 1 liver abscess, 1 cholecystitis, 1 urosepsis), ascites (25%), stroke (10%), variceal bleeding (6%), hepatic encephalopathy (6%), and heart attack (3%). CFS was worse in case of higher Child-Pugh scores and higher BCLC stages (supplementary Figs. 5 and 6). Concerning our confounding variables, age was independently associated with CFS in uni- and multivariable analyses, while BCLC stage ($p = 0.083$) and AFP ($p = 0.092$) approached significance. Concerning our main variables of interest, reduced HGS was the only parameter of nutritional status significantly associated with CFS In univariable Cox regression analysis (Table 3).

The association between HGS and CFS in univariable Kaplan Meier analysis is shown in Fig. 2.

In multivariable analyses with correction for the confounders for BCLC stage, AFP and age, reduced HGS remained significantly associated with CFS (HR = 0.304, 95% CI 0.105–0.881; $p = 0.028$: Table 3).

3.5. Progression-free survival: association with baseline parameters

Of the patients who recieved tumor-specific therapy, tumor progression or death occurred in 32 cases (67%) during follow-up, with a median PFS time of 225 (range 56 –962) days. in uni- and multivariable analyses, BCLC stage and age were independently associated with PFS, while AFP ($p = 0.09$) was approaching significance. There was no association between any of the parameters of nutritional state at baseline and PFS, in either univariable or multivariable analyses.

3.6. Repeated measurements three months after tumor-specific therapy

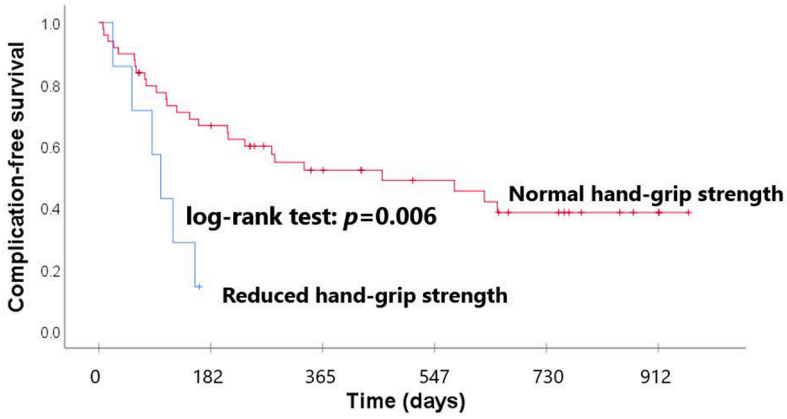
Of all patients, 10% received best supportive care. The other 50 patients received various initial treatments, both with curative intent (20% radiofrequency ablation/ microwave ablation, 4% resection) and with palliative intent (50% transarterial radioembolization, 24% transarterial chemoembolization, 2% sorafenib). As far as transarterial radioembolization is concerned, 16 patients were treated with holmium-166 in a phase 2 study [43], the remaining patients with Yttrium-90. Four patients received additional treatment after the 3 months post-treatment evaluation: two patients underwent liver transplantation, one patient received additional transarterial chemoembolization, and one patient received additional transarterial radioembolization. Repeated nutritional measurements three months post-treatment were available in 38 of the 50 patients (76%) who received antitumor therapy (flowchart Supplementary Fig. 1). Their patient and tumor characteristics at baseline and at 3 months post-treatment follow up are given in Table 4.

There were no significant differences in patient and tumor characteristics between these 38 patients and the entire group of 50 patients. For Child-Pugh scores and tumor response according to mRECIST, 3-month data were available in 49 and 45 cases.

At the evaluation 3 months post-treatment, complete response according to mRECIST was obtained in 44%, partial response in 20%, stable disease in 20% and progressive disease in 16%. In uni- and multivariable Cox-regression analyses in all 45 patients with 3-month post-treatment mRECIST scores available, tumor response according to mRECIST at 3 months post-treatment was independently associated with PFS ($p<0.001$) but not with OS or CFS.

Baseline Child-Pugh stages were A in 90% and B 10% versus A in 71% and B in 26% three months post-treatment ($p = 0.058$). In uni- and multivariable Cox-regression analyses in all 49 patients with 3-month post-treatment Child-Pugh scores available, deterioration of Child-Pugh score at 3 months post-treatment was independently associated with worse OS and CFS (Tables 2 and 3). Type of anti-tumor therapy (transarterial radioembolization vs other treatment) did not influence these associations. Kaplan-Meier curves showed significantly reduced OS and CFS in patients with deteriorated Child-Pugh scores (log-rank test: $P<0.001$: Supplementary Figs. 7 and 8).

In most cases, repeated CT-scans three-months post-treatment were



At risk (n)	56	31	19	14	9	3
Normal	49	31	19	14	9	3
Low	7	0	0	0	0	0

Fig. 2. Kaplan-Meier curve shows reduced complication-free survival in patients with reduced handgrip strength (log-rank test: $p = 0.006$).

not available, precluding further analyses on (change of) L3-SMI at this time point. The other nutritional parameters deteriorated. No patient improved from reduced HGS at baseline to normal HGS post-treatment. Only one patient improved (from frail to prefrail) according to LFI between baseline and follow-up. As far as LFI is concerned, the patients were therefore divided into two groups (deterioration versus equal and improvement combined). There was no relation between change of nutritional parameters and OS (Table 2). A change in LFI score was independently associated with CFS, which was not the case for the other nutritional parameters (Table 3). Change of the nutritional parameters at 3 months post-treatment was not related to PFS.

4. Discussion

Despite the introduction of several new treatment modalities for HCC in the last decades, prognosis remains poor. Impaired nutritional status is a frequent phenomenon in patients with HCC. If impaired nutritional status could be identified with the aid of etiological modeling studies, as a risk factor causally related to poor outcome, further research as to whether early nutritional support could aid in improving survival and quality of life, would be indicated. In our study with etiological multivariable analyses [41,42], reduced HGS was significantly associated with CFS and nearly reached significance for the association with OS ($p = 0.052$) (in line with a previous report [27]). Our data also suggest that HGS could be used as an easy – to – use tool that could aid in accurate predicting survival in HCC patients. In this respect it is relevant that currently, MRI-scan rather than CT-scan is the preferred imaging modality for HCC diagnosis and follow up. MRI-scan is less validated than CT-scan for assessment of sarcopenia risk. CT-scan only to determine CT L3-SMI requires patient time, commercial software, increases costs and is associated with a small risk. HGS is independently associated with mortality in various conditions including cardiovascular disease [44] and hemodialysis [45]. HGS has been suggested as a biomarker of aging across the life course and to predispose for fatal outcome in presence of various diseases [44,46]. Unlike HGS, LFI and PG-SGA did not seem to be associated with survival. It is not surprising, that HGS, LFI, PG-SGA and L3-SMI yielded quite different outcomes. These investigations yield complementary valuable information on muscle strength, muscle quantity and quality, loss of physiological reserve with increased vulnerability and malnutrition. Interestingly, our results indicate that impaired LFI and PG-SGA were associated with worse quality of life, which was not the case for HGS or L3-SMI.

An important finding of our study was that decrease of liver function (according to Child-Pugh score) at 3 months post-treatment was independently associated with worse overall and complication-free survival. Although decreased liver function could be due to tumor progression, potential negative effects of the anti-tumor treatment itself could also have contributed. Similarly, a recent study comparing transarterial radioembolization and sorafenib with the aid of propensity score matching analyses [47] identified decreased liver function after the radioembolization as an important negative prognostic factor. In that study, only liver decompensation occurring longer than four months post-treatment was taken into account (with the rationale to exclude earlier decompensation due to radiation-induced liver disease). Our data suggest that earlier decompensation also has a negative effect on clinical course and that this phenomenon is not restricted to transarterial radioembolization. These findings stress the importance to avoid treatment-related liver injury. New approaches for transarterial radioembolization such as personalized treatment planning based on dosimetry instead of a predefined average absorbed dose in the perfused volume could aid to avoid liver injury [48].

Strengths of the current study are its prospective design and the baseline evaluation of nutrition disorders and nutrition-related conditions. Also, the variables of interest were corrected in the multivariable analyses of this etiologic modeling study, for BCLC stage, AFP and age, considering the established considerable impact of these three confounders on outcome in hepatocellular carcinoma. In the statistical approach of previous studies on nutritional status in HCC patients, prerequisites for etiological modeling were generally not taken into account or nor clearly reported [41,42]. Limitations of our work are the heterogenous anti-tumor treatment modalities and the relatively small patients numbers. Especially for the nutritional assessments 3 months post-treatment, patient numbers were limited. We therefore cannot exclude a type II error for our finding that change of nutritional parameters was in general not associated with outcome (Tables 2 and 3). Also, in our study, CT-scan at baseline was only performed if clinically indicated and only rarely at follow-up. Therefore, definite conclusions about the value of CT-scan - derived L3-SMI cannot be drawn from the current work. Of note, we chose age-bound, sex-specific reference values for HGS, where we considered a value below the 10th percentile as reduced HGS [39]. Higher cut-off point for reduced HGS would theoretically lead to higher sensitivity but lower specificity. Finally, the

Table 4
Clinical characteristics of 38 hepatocellular carcinoma patients with measurements of nutritional status available at baseline and 3 months after the first tumor treatment.

All patients	Baseline (n = 38)	3 months after first treatment (n = 38)	p-value
Age (years)	72 ± 7 (48 – 86)		
Male gender	35 (92)		
Etiology			
HBV	2 (5)		
HCV	4 (11)		
NAFLD/NASH	12 (32)		
Alcohol	13 (34)		
Hemochromatosis	1 (3)		
Other	1 (3)		
Unknown	5 (12)		
Cirrhotic[a]	32 (84)		
Fibroscan[b]			
F0–2	2 (15)		
F3–4	11 (85)		
Treatment[c]			
Resection	2 (5)		
RFA/MWA	6 (16)		
TACE	11 (29)		
TARE	19 (50)		
Creatinine (μmol/L)	82 ± 26 (32 – 138)	82 ± 27 (34 – 145)	0.518
Total bilirubin (μmol/L)	14 (4 – 31)	15 (4 – 46)	0.959
Alkaline phosphatase (U/L)	107 (46 – 330)	129 (60 – 933)	0.070
Gamma-GT (U/L)	163 (35 – 1080)	136 (26– 1150)	0.167
ASAT (U/L)	47 (16 – 590)	40 (15 – 497)	**0.053**
ALAT (U/L)	39 (11 –224)	32 (10 – 270)	**0.023***
Albumin (g/L)	39 ± 4 (28 – 50)	36 ± 5 (23 – 44)	**0.002***
Thrombocytes (x10^9/L)	148 (40 – 694)	129 (34 – 405)	**0.072**
PT-INR	1.14 (1.00 – 1.84)	1.13 (1.00 – 5.50)	0.943
Sodium (mmol/L)	138 ± 3 (132 – 144)	138 ± 3 (131 – 143)	0.731
Alpha-fetoprotein (mcg/L)	10 (2 – 12,100)	7 (2 – 4400)	0.295
Portal hypertension	26 (68)		
Varices	15 (40)		
Collaterals	22 (58)		
Thrombocytopenia	18 (47)		
Ascites			
Absent	31 (81)	29 (76)	0.470
Slight	6 (16)	5 (13)	
Moderate	1 (3)	3 (8)	
n/a	0(0)	1 (3)	
Hepatic encephalopathy			
No	38 (100)	36 (94)	0.317
Grade 1–2	0 (0)	1 (3)	
n/a	0 (0)	1(3)	
Dialysis			
No	38 (100)	37 (97)	1.000
n/a	0 (0)	1(3)	
Child-Pugh score	5 (5 – 7)	6 (5 – 8)	**0.026***
Child-Pugh stage			
A (5–6)	34 (90)	27 (71)	**0.058**
B (7–9)	4 (10)	10 (26)	
n/a	0(0)	1 (3)	
MELD-score	9 (6 – 20)	9 (6 – 31)	**0.059**
MELD-Na score	11 (7 – 20)	11 (7 – 31)	0.134
Performance score (ECOG)			
0	25 (66)	18 (47)	**0.026***
1	10 (26)	12 (32)	
2	3 (8)	6 (16)	
3	0 (0)	2 (5)	
mRECIST			
Complete response	-	17 (45)	
Partial response	-	9 (24)	
Stable disease	-	8 (21)	
Progressive disease	-	4 (10)	
BMI (kg/m^2)	28 (20 – 41)	27 (22 – 41)	0.232
Weight (T0) (kg)	90 ± 18 (50 – 136)	89 ± 18 (54 – 133)	0.189
ΔWeight 1 month before T0 – T0 (kg)	0 (−33 – +2)	–	**0.003***
ΔWeight 6 months before T0 – T0 (kg)	−2 (−17 – +8)	–	0.939
PG-SGA total score	4 (1 – 13)	5 (1 – 19)	0.069
PG-SGA stage			0.197
A well nourished	29 (76)	25 (66)	
B moderate malnourished	9 (24)	12 (31)	
C severe malnourished	0 (0)	1 (3)	
Liver frailty index score	3.94 (2.46 – 6.33)	4.05 (3.27 – 6.78)	**0.004***
Liver frailty index			**0.059**
Robust	3 (8)	0 (0)	
Prefrail	29 (76)	30 (79)	
Frail	6 (16)	7 (18)	
n/a	0 (0)	1 (3)	
Handgrip strength			
Highest (kg)	34 ± 9 (16 – 50)	31 ± 8 (11 – 43)	**<0.001***
Reduced	5 (13)	8 (21)	0.083
Chairtest[d]			
Time (s)	13 (7 – 29)	13 (8 – 25)	0.673
Prolonged	5 (13)	9 (24)	0.102
CT-scan L3[e]			
Skeletal muscle index	46.5 ± 7.1		
Sarcopenia risk	(31.1–65.0) 20 (79)		
EORTC-QLQ C30 Global health status (C30)	75 (33 – 100)	75 (8 – 100)	0.811
Summary score QoL (C30)	91 (49 – 100)	87 (43 – 100)	**0.034***
Summary score QoL (HCC18)	8 (0–48)	11 (0–53)	**0.044***
Death during follow-up	16 (42)		
Duration of follow-up (days)	461 (65–962)		
Progression during follow-up	24 (63)		

Data are presented as n (%), in case of parametric distribution as mean ± SD (range) or in case of nonparametric distribution as median (range). n/a not available. * p-value <0.05.

[a] Based on clinical, radiologic or histologic data.

[b] Fibroscan was performed in 13/38 patients (34%).

[c] 1 patient received liver transplantation 20 months after initial TACE.

[d] 5/38 patients (13%)at baseline and 6/38 (16%) at follow-up were not able to perform or complete the chair test in less than 60 s and were not included.

[e] Baseline CT-scan available in 28/38 patients (74%).

included patients were a selected group of patients, mostly in good condition, referred for potential anti-tumor therapy to a tertiary care center with special interest in transarterial radioembolisation. Early dietary intervention could be especially effective in this patient group. Our results may not be generalizable to HCC patients with end stage (BCLC-D) HCC.

In conclusion, impaired nutritional status occurs frequently in patients with hepatocellular carcinoma. Reduced baseline hand-grip strength and deteriorated Child-Pugh score 3 months after anti-tumor treatment were associated with reduced overall and complication-free survival in HCC patients. Whereas avoiding treatment-related liver injury should certainly be pursued, the potential value of dietary interventions to improve outcome in selected HCC patients remains to be explored.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Acknowledgement

The authors thank C-P. L. van Erpecum for expert statistical advice.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.07.002.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49. https://doi.org/10.3322/caac.21660.

[2] Bunchorntavakul C, Reddy KR. Review article: malnutrition/sarcopenia and frailty in patients with cirrhosis. Aliment Pharmacol Ther 2020;51:64–77. https://doi.org/10.1111/apt.15571.

[3] Lai JC, Covinsky KE, McCulloch CE, Feng S. The liver frailty index improves mortality prediction of the subjective clinician assessment in patients with cirrhosis. Am J Gastroenterol 2018;113:235–42. https://doi.org/10.1038/ajg.2017.443.

[4] Wang S, Whitlock R, Xu C, Taneja S, Singh S, Abraldes JG, et al. Frailty is associated with increased risk of cirrhosis disease progression and death. Hepatology 2022;75:600–9. https://doi.org/10.1002/hep.32157.

[5] Sieber CC. Malnutrition and sarcopenia. Aging Clin Exp Res 2019:793–8. https://doi.org/10.1007/s40520-019-01170-1.

[6] Huisman EJ, Trip EJ, Siersema PD, Van Hoek B, Van Erpecum KJ. Protein energy malnutrition predicts complications in liver cirrhosis. Eur J Gastroenterol Hepatol 2011;23:982–9. https://doi.org/10.1097/MEG.0b013e32834aa4bb.

[7] Montano-Loza AJ. Clinical relevance of sarcopenia in patients with cirrhosis. World J Gastroenterol 2014;20:8061–71. https://doi.org/10.3748/wjg.v20.i25.8061.

[8] Kroh A, Uschner D, Lodewick T, Eickhoff RM, Schöning W, Ulmer FT, et al. Impact of body composition on survival and morbidity after liver resection in hepatocellular carcinoma patients. Hepatobiliary Pancreat Dis Int 2019;18:28–37. https://doi.org/10.1016/j.hbpd.2018.07.008.

[9] Akce M, Liu Y, Zakka K, Martini DJ, Draper A, Alese OB, et al. Impact of sarcopenia, BMI, and inflammatory biomarkers on survival in advanced hepatocellular carcinoma treated with anti-PD-1 antibody. Am J Clin Oncol Cancer Clin Trials 2021;44:74–81. https://doi.org/10.1097/COC.0000000000000787.

[10] Marasco G, Serenari M, Renzulli M, Alemanni LV, Rossini B, Pettinari I, et al. Clinical impact of sarcopenia assessment in patients with hepatocellular carcinoma undergoing treatments. J Gastroenterol 2020;55:927–43. https://doi.org/10.1007/s00535-020-01711-w.

[11] Meza-Junco J, Montano-Loza AJ, Baracos VE, Prado CMM, Bain VG, Beaumont C, et al. Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma. J Clin Gastroenterol 2013;47:861–70. https://doi.org/10.1097/MCG.0b013e318293a825.

[12] Fujiwara N, Nakagawa H, Kudo Y, Tateishi R, Taguri M, Watadani T, et al. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. J Hepatol 2015;63:131–40. https://doi.org/10.1016/j.jhep.2015.02.031.

[13] Chang KV, De Chen J, Wu WT, Huang KC, Hsu CT, Han DS. Association between loss of skeletal muscle mass and mortality and tumor recurrence in hepatocellular carcinoma: a systematic review and meta-analysis. Liver Cancer 2018;7:90–103. https://doi.org/10.1159/000484950.

[14] Begini P, Gigante E, Antonelli G, Carbonetti F, Iannicelli E, Anania G, et al. Sarcopenia predicts reduced survival in patients with hepatocellular carcinoma at first diagnosis. Ann Hepatol 2017;16:107–14. https://doi.org/10.5604/16652681.1226821.

[15] Badran H, Elsabaawy MM, Ragab A, Aly RA, Alsebaey A, Sabry A. Baseline sarcopenia is associated with lack of response to therapy, liver decompensation and high mortality in hepatocellular carcinoma patients. Asian Pac J Cancer Prev 2020;21:3285–90. https://doi.org/10.31557/APJCP.2020.21.11.3285.

[16] Iritani S, Imai K, Takai K, Hanai T, Ideta T, Miyazaki T, et al. Skeletal muscle depletion is an independent prognostic factor for hepatocellular carcinoma. J Gastroenterol 2015;50:323–32. https://doi.org/10.1007/s00535-014-0964-9.

[17] Zhang G, Meng S, Li R, Ye J, Zhao L. Clinical significance of sarcopenia in the treatment of patients with primary hepatic malignancies, a systematic review and meta-analysis. Oncotarget 2017;8:102474–85. https://doi.org/10.18632/oncotarget.19687.

[18] Schütte K, Tippelt B, Schulz C, Röhl FW, Feneberg A, Seidensticker R, et al. Malnutrition is a prognostic factor in patients with hepatocellular carcinoma (HCC). Clin Nutr 2015;34:1122–7. https://doi.org/10.1016/j.clnu.2014.11.007.

[19] Voron T, Tselikas L, Pietrasz D, Pigneur F, Laurent A, Compagnon P, et al. Sarcopenia impacts on short- and long-term results of hepatectomy for hepatocellular carcinoma. Ann Surg 2015;261:1173–83. https://doi.org/10.1097/SLA.0000000000000743.

[20] Harimoto N, Shirabe K, Yamashita YI, Ikegami T, Yoshizumi T, Soejima Y, et al. Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. Br J Surg 2013;100:1523–30. https://doi.org/10.1002/bjs.9258.

[21] Takagi K, Yagi T, Yoshida R, Shinoura S, Umeda Y, Nobuoka D, et al. Sarcopenia and American society of anesthesiologists physical status in the assessment of outcomes of hepatocellular carcinoma patients undergoing hepatectomy. Acta Med Okayama 2016;70:363–70. https://doi.org/10.18926/AMO/54594.

[22] Xu L, Jing Y, Zhao C, Zhang Q, Zhao X, Yang J, et al. Preoperative computed tomography-assessed skeletal muscle index is a novel prognostic factor in patients with hepatocellular carcinoma following hepatectomy: a meta-analysis. J Gastrointest Oncol 2020;11:1040–53. https://doi.org/10.21037/jgo-20-122.

[23] Levolger S, Van Vledder MG, Muslem R, Koek M, Niessen WJ, De Man RA, et al. Sarcopenia impairs survival in patients with potentially curable hepatocellular carcinoma. J Surg Oncol 2015;112:208–13. https://doi.org/10.1002/jso.23976.

[24] Salman A, Salman M, Moustafa A, Shaaban HE-D, El-Mikkawy A, Labib S, et al. Impact of sarcopenia on two-year mortality in patients with HCV-associated hepatocellular carcinoma after radiofrequency ablation. J Hepatocell Carcinoma 2021;8:313–20. https://doi.org/10.2147/jhc.s300680.

[25] Antonelli G, Gigante E, Iavarone M, Begini P, Sangiovanni A, Iannicelli E, et al. Sarcopenia is associated with reduced survival in patients with advanced hepatocellular carcinoma undergoing sorafenib treatment. United Eur Gastroenterol J 2018;6:1039–48. https://doi.org/10.1177/2050640618781188.

[26] Nishikawa H, Nishijima N, Enomoto H, Sakamoto A, Nasu A, Komekado H, et al. Prognostic significance of sarcopenia in patients with hepatocellular carcinoma undergoing sorafenib therapy. Oncol Lett 2017;14:1637–47. https://doi.org/10.3892/ol.2017.6287.

[27] Endo K, Kuroda H, Kanazawa J, Sato T, Fujiwara Y, Abe T, et al. Impact of grip strength in patients with unresectable hepatocellular carcinoma treated with lenvatinib. Cancers 2020;12:2146. https://doi.org/10.3390/cancers12082146 (Basel).

[28] Lanza E, Masetti C, Messana G, Muglia R, Pugliese N, Ceriani R, et al. Sarcopenia as a predictor of survival in patients undergoing bland transarterial embolization for unresectable hepatocellular carcinoma. PLoS ONE 2020;15:e0232371. https://doi.org/10.1371/journal.pone.0232371.

[29] Lee J, Cho Y, Park S, Kim JW, Lee IJ. Skeletal muscle depletion predicts the prognosis of patients with hepatocellular carcinoma treated with radiotherapy. Front Oncol 2019;9:1075. https://doi.org/10.3389/fonc.2019.01075.

[30] Lai JC, Tandon P, Bernal W, Tapper EB, Ekong U, Dasarathy S, et al. Malnutrition, frailty, and sarcopenia in patients with cirrhosis: 2021 practice guidance by the American association for the study of liver diseases. Hepatology 2021;74:1611–44. https://doi.org/10.1002/hep.32049.

[31] Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:601. https://doi.org/10.1093/ageing/afy169.

[32] Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, et al. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology 2017;66:564–74. https://doi.org/10.1002/hep.29219.

[33] Jager-Wittenaar H, Ottery FD. Assessing nutritional status in cancer: role of the patient-generated subjective global assessment. Curr Opin Clin Nutr Metab Care 2017;20:322–9. https://doi.org/10.1097/MCO.0000000000000389.

[34] Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul JL, et al. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182–236. https://doi.org/10.1016/j.jhep.2018.03.019.

[35] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76. https://doi.org/10.1093/jnci/85.5.365.

[36] Blazeby JM, Currie E, Zee BCY, Chie W-C, Poon RT, Garden OJ. Development of a questionnaire module to supplement the EORTC QLQ-C30 to assess quality of life in patients with hepatocellular carcinoma, the EORTC QLQ-HCC18. Eur J Cancer 2004;40:2439–44. https://doi.org/10.1016/j.ejca.2004.06.033.

[37] Li L, Mo FKF, Chan SL, Hui EP, Tang NSL, Koh J, et al. Prognostic values of EORTC QLQ-C30 and QLQ-HCC18 index-scores in patients with hepatocellular carcinoma - clinical application of health-related quality-of-life data. BMC Cancer 2017;17:8. https://doi.org/10.1186/s12885-016-2995-5.

[38] Carey EJ, Lai JC, Wang CW, Dasarathy S, Lobach I, Montano-Loza AJ, et al. A multicenter study to define sarcopenia in patients with end-stage liver disease. Liver Transpl 2017;23:625–33. https://doi.org/10.1002/lt.24750.

[39] Dodds RM, Syddall HE, Cooper R, Benzeval M, Deary IJ, Dennison EM, et al. Grip strength across the life course: normative data from twelve British studies. PLoS ONE 2014;9:e113637. https://doi.org/10.1371/journal.pone.0113637.

[40] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52–60. https://doi.org/10.1055/s-0030-1247132.

[41] van Diepen M, Ramspek CL, Jager KJ, Zoccali C, Dekker FW. Prediction versus aetiology: common pitfalls and how to avoid them. Nephrol Dial Transplant 2017;32:ii1–5. https://doi.org/10.1093/ndt/gfw459. Off Publ Eur Dial Transpl Assoc Eur Ren Assoc.

[42] Ramspek CL, Steyerberg EW, Riley RD, Rosendaal FR, Dekkers OM, Dekker FW, et al. Prediction or causality? A scoping review of their conflation within current observational research. Eur J Epidemiol 2021;36:889–98. https://doi.org/10.1007/s10654-021-00794-w.

[43] Reinders MTM, van Erpecum KJ, Smits MLJ, Braat AJAT, de Bruijne J, Bruijnen RCG, et al. Safety and efficacy of holmium-166 radioembolization in

hepatocellular carcinoma - the HEPAR Primary study. J. Nucl. Med. 2022. https://doi.org/10.2967/jnumed.122.263823. Online ahead of print.PMID: 35589409.
[44] Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum AJ, Orlandini A, et al. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. Lancet 2015;386:266–73. https://doi.org/10.1016/S0140-6736(14)62000-6.
[45] Hwang SH, Lee DH, Min J, Jeon JY. Handgrip strength as a predictor of all-cause mortality in patients with chronic kidney disease undergoing dialysis: a meta-analysis of prospective cohort studies. J Ren Nutr 2019;29:471–9. https://doi.org/10.1053/j.jrn.2019.01.002. Off J Counc Ren Nutr Natl Kidney Found.
[46] Sayer AA, Kirkwood TBL. Grip strength and mortality: a biomarker of ageing? Lancet 2015;386:226–7. https://doi.org/10.1016/S0140-6736(14)62349-7.
[47] van Doorn DJ, Hendriks P, Burgmans MC, Rietbergen DDD, Coenraad MJ, van Delden OM, et al. Liver decompensation as late complication in HCC patients with long-term response following selective internal radiation therapy. Cancers 2021;13:5427. https://doi.org/10.3390/cancers13215427 (Basel).
[48] Garin E, Tselikas L, Guiu B, Chalaye J, Edeline J, de Baere T, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol Hepatol 2021;6:17–29. https://doi.org/10.1016/S2468-1253(20)30290-9.