Cachexia is Prevalent in Patients with Hepatocellular Carcinoma and Associated with Worse Prognosis

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Abstract

Background: Cancer cachexia is a wasting syndrome associated with functional impairment and reduced survival that impacts up to 50% of patients with gastrointestinal cancers. However, data are limited on the prevalence and clinical significance of cachexia in patients with hepatocellular carcinoma (HCC).

Methods: We performed a retrospective cohort study of patients diagnosed with HCC at two U.S. health systems between 2008 – 2018. Patient weights were recorded six months prior and at HCC diagnosis. Cachexia was defined as >5% weight loss (or >2% weight loss if BMI <20 kg/m^2) and precachexia defined as 2–5% weight loss. We used multivariable logistic regression models

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Conflicts of Interest: Jorge Marrero has served as a consultant for Glycotest and received research funding from AstraZeneca. Amit Singal has been on advisory boards and served as a consultant for Wako Diagnostics, Roche, Exact Sciences, Glycotest, GRAIL, Bayer, Eisai, Exelixis, BMS, AstraZeneca, Genentech, and TARGET-RWE. Pfizer, Inc. is currently supporting a collaborative project with the laboratory of Rodney Infante that is independent of all data presented in this manuscript. The other authors have no relevant conflicts of interest.

to identify correlates of cachexia and multivariable Cox proportional hazard models to identify factors associated with overall survival.

Results: Of 604 patients with HCC, 201 (33.3%) had precachexia and 143 (23.7%) had cachexia at diagnosis, including 19.0%, 23.5%, 34.7%, and 34.0% of patients with BCLC stages 0/A, B, C, and D, respectively. Patients with cachexia were less likely to receive HCC treatment (OR 0.38, 95%CI 0.21 – 0.71) and had worse survival than those with precachexia or stable weight (11.3 vs 20.4 vs 23.5 months, respectively, p<0.001). Cachexia remained independently associated with worse survival (HR 1.43, 95%CI 1.11 – 1.84) after adjusting for age, sex, race/ethnicity, Child Pugh class, AFP, BCLC stage and HCC treatment.

Conclusions: Nearly 1 in 4 patients with HCC present with cachexia, including many with compensated cirrhosis or early-stage tumors. The presence of cancer-associated weight loss appears to be an early and independent predictor of worse outcomes in patients with HCC.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fastest rising cause of cancer-related death in the U.S. It is unique among malignancies, in that the majority of cases occur in the background of a diseased organ, the cirrhotic liver.[1, 2] The most commonly used staging system in HCC -- the Barcelona Clinic Liver Cancer (BCLC) staging system – includes not only the patient's tumor burden but also their degree of liver dysfunction and performance status, measured using the Eastern Cooperative Oncology Group (ECOG) scale. Prior studies have demonstrated the impact of sarcopenia and functional status on survival in HCC[3–5]. In parallel, frailty has emerged as an important predictor of prognosis in patients with cirrhosis (including those without HCC) [6–8], and objective measures of performance status and frailty are increasingly being utilized in this population for prognostication and therapeutic decision-making, including liver transplant eligibility.[6]

Cancer cachexia is a related but distinct clinical syndrome of wasting, characterized by the ongoing loss of adipose tissue and skeletal muscle mass, leading to progressive functional impairment.[9] The mechanism of cachexia is multifactorial and not merely related to caloric deficiency, but in part driven by systemic inflammation and tumor-secreted factors leading to abnormal metabolism.[10–13] It is considered to exist along a continuum with three clinical phases (precachexia, cachexia, and refractory cachexia) and is objectively defined based on percentage of total body weight lost (i.e., patients with >5% weight loss [or >2% weight loss for patients with BMI <20 mg/kg^2] over a 6 month period are classified as having cachexia, per international consensus definition).[9] Cachexia is common, occurring in approximately 50% of patients with cancer[11, 14, 15], including those with other gastrointestinal malignancies (e.g., pancreatic[16], esophageal[17], colon cancers[15]). It is associated with impaired physical function[18], poorer quality of life, lower rates of treatment response, and worse overall survival.[15, 16] As cachexia in patients with cancer is often

underrecognized and undertreated, earlier recognition and management of this syndrome may lead to improved quality of life and survival outcomes.

While cachexia has been shown to be an important prognostic indicator in other cancers[15], its prevalence and clinical significance in patients with HCC remain unknown. To our knowledge, no prior studies have applied the international consensus definition of cancer cachexia to a well-characterized patient population with cirrhosis and HCC. Therefore, we aimed to comprehensively evaluate the prevalence, correlates and prognostic impact of cachexia in patients with HCC.

METHODS

Study Cohort

We identified consecutive patients diagnosed with HCC between January 2008 and December 2018 at two large U.S. health systems, the University of Texas (UT) Southwestern Medical Center and Parkland Health and Hospital System, using our prospectively maintained institutional database. All HCC diagnoses were confirmed on chart review using the AASLD guidelines, i.e. characteristic imaging findings (LI-RADS 5) or histology.[19] We excluded patients lacking weight data at time of HCC diagnosis (+/− 1 month), as well as patients with detectable ascites on imaging 6 months prior to HCC diagnosis. Patients without characteristic imaging or histology confirming HCC diagnosis, patients in whom the date of initial HCC diagnosis could not be ascertained from review of the electronic medical record (EMR), and patients who received HCC treatment at an outside facility prior to presentation at one of the study sites were also excluded. This study was approved by the Institutional Review Board of the UT Southwestern Medical Center.

Data Collection

We abstracted relevant demographic, laboratory, and imaging data at time of HCC diagnosis from the EMR. The date of HCC diagnosis was defined as date at which lesions met HCC criteria per AASLD guidelines.[19] Demographic factors including age, race, ethnicity, and gender were obtained through self-report from each patient at initial clinic visit.[20, 21] Insurance status was recorded from the EMR and categorized as private insurance, Medicaid, Medicare, other (including Parkland's subsidy program for medical care) or no insurance. Clinical variables of interest included ECOG performance status abstracted from clinical notes, presence of cirrhosis (defined by: 1) histopathology indicating F4 disease; 2) serum or radiologic markers of fibrosis consistent with cirrhosis; 3) imaging with nodular liver and signs of portal hypertension; or 4) platelet count less than 150,000 in the setting of chronic liver disease), etiology of cirrhosis (classified as hepatitis C virus, hepatitis B virus, alcohol-related liver disease, and nonalcoholic fatty liver disease)[22], and degree of liver dysfunction (Child Pugh score). The presence of encephalopathy and/or ascites at time of HCC diagnosis was classified as none, mild/controlled, or severe/uncontrolled. Laboratory data at diagnosis included total bilirubin, international normalized ratio, albumin, platelet count, creatinine, and alpha fetoprotein (AFP).

Tumor characteristics were determined via imaging, and all tumors were staged using the BCLC staging system.[23] All HCC-directed treatments were recorded; if a patient received multiple HCC treatments, the treatments were ranked as "most definitive" as described previously,[20] i.e., liver transplantation > surgical resection > local ablation (e.g. radiofrequency or microwave ablation) > stereotactic body radiation therapy (SBRT) > transarterial chemoembolization (TACE) or transarterial radioembolization (TARE) > systemic therapy > best supportive care (BSC). Curative treatment was defined as liver transplantation, surgical resection, or local ablative therapy. Survival was calculated from date of HCC diagnosis to date of death, with patients censored at last known follow-up or liver transplantation.

Definition of Cancer Cachexia and Assessment of HCC-Associated Weight Loss

Two authors (N.D. and S.M.) manually recorded patient weights at HCC diagnosis and 6 months prior to HCC diagnosis; weights were included if available +/− 1 month within the date of interest. In both health systems, weight is routinely recorded in the EMR at each clinic visit and during all hospital stays. Each patient's height was also recorded for calculation of body mass index (BMI). The presence of ascites on imaging and/or use of diuretics was captured at the same time points. Weight loss was defined as the percentage of total body weight lost and classified according to previously validated, international consensus definitions. Cachexia was defined as >5% weight loss (or weight loss >2% in patients with BMI <20 kg/m^2) over a 6 month period, whereas precachexia was defined as minimal unintentional weight loss not meeting the criteria for cachexia (i.e., <5% weight loss).[9]

Statistical Analysis

Demographic, clinical, and tumor characteristics are reported using descriptive statistics, stratified by presence of cachexia. Categorical variables were compared using Chi-square and Fisher's exact tests, while continuous variables were compared using the Kruskal-Wallis test. We used logistic regression models to identify correlates of cachexia. Univariable and multivariable Cox proportional hazard models were utilized to identify factors associated with overall survival. Log-rank tests were used to compare survival distributions between groups. Multivariable models were adjusted for factors determined *a priori* to be associated with HCC prognosis (e.g., Child Pugh score) and those significant in univariate analyses (p< 0.20). All multivariable analyses were 2-sided and performed with a 5% significance level. Statistical analysis was performed utilizing Stata 16.1 (StataCorp, College Station, TX).

RESULTS

Patient Characteristics

Clinical characteristics of the 604 patients at time of HCC diagnosis are summarized in Table 1. Median age was 60.9 years, 72.2% were male, and over half (56.2%) had Child Pugh class A cirrhosis. The cohort was diverse with regard to race/ethnicity (32.1% White, 34.1% Black, 29.0% Hispanic) and tumor stage (58.6% BCLC stage A, 16.3% B, 16.8% C, and 8.3% stage D).

Prevalence and Correlates of Cachexia

At time of HCC diagnosis, 143 (23.7%) patients had cachexia, including 19.0%, 23.5%, 34.7%, and 34.0% of patients with BCLC stage 0/A, B, C, and D HCC, respectively (Figure 1). Precachexia was observed in 201 (33.3%) patients, and 260 (43.0%) patients had either stable or increased weight. As expected, BMI at HCC diagnosis was lower in patients with cachexia compared to those with pre-cachexia or stable weight, (median BMI 25.4, 28.3, and 28.5, respectively). The proportion of patients with cachexia was similar by sex (p=0.09), race/ethnicity (p=0.62) and age (p=0.42). In univariable analyses (Table 2), pre-treatment cachexia was associated with ECOG performance status 2, Child Pugh class B/C cirrhosis, presence of ascites, presence of encephalopathy, AFP >200 ng/mL, tumor size >5 cm, and BCLC stage C or D disease. The presence of pre-treatment cachexia remained significantly associated with Child Pugh class B/C cirrhosis and tumor size >5 cm on multivariable analyses.

Among the subset of patients (n=335) with preserved liver function (Child Pugh A) and performance status (ECOG 0–1), cachexia was present in 17.3% of patients – including 12.7%, 25.4%, and 30.4% of patients with BCLC stage 0/A, B, and C HCC, respectively. Similarly, when we examined the subset of patients with no prior history of ascites or diuretic use (n=363), cachexia was present in 16.7% of patients – including 11.1%, 24.2%, 25.0% and 66.7% of patients with BCLC stage 0/A, B, C, and D HCC, respectively.

Cachexia and HCC Treatment Receipt

Patients with cachexia were less likely to receive HCC treatment compared to those without cachexia (OR 0.30, 95% CI 0.19 – 0.50). Results were consistent in multivariable analyses after adjusting for age, sex, race/ethnicity, Child Pugh class and BCLC tumor stage (OR 0.38, 95% CI 0.21 – 0.71). Similarly, patients with cachexia were less likely to receive curative HCC treatment (OR 0.48, 95% CI 0.31 – 0.73) compared to those without cachexia, however this relationship was no longer statistically significant in multivariable analyses (OR 0.71, 95% CI 0.42 – 1.19). Of note, results were similar in both analyses when we adjusted for MELD score, ascites, and encephalopathy in the multivariable models rather than Child Pugh class.

When patients with precachexia were compared to those with stable weight, there was no significant difference in overall treatment receipt (OR 0.99, 95% CI 0.52 – 1.89) or curative treatment receipt (OR 0.98, 95% CI 0.62 – 1.55) in multivariable analyses.

Cachexia and Overall Survival

Median overall survival for all patients was 19.7 months (interquartile range [IQR] 7.1 – 57.5 months). Overall survival, stratified by presence of cachexia, is shown in Figure 2. Patients with cachexia had median overall survival of 11.3 months (IQR 3.7 – 34.5 months) compared to 20.4 months (IQR 6.9 – 62.4 months) and 23.5 months (9.9 – 61.5 months) in patients with pre-cachexia and those with stable weight, respectively (p<0.001). Survival differences between patients with cachexia, precachexia, and stable weight were consistent across BCLC stages and Child Pugh classes (Figures 2 and 3), as well as by subgroups of sex, race/ethnicity, BMI category, and most definitive HCC treatment type (Supplemental

Table 1). In multivariable analyses, after adjusting for age, sex, race, Child Pugh class, AFP, BCLC tumor stage and HCC treatment received, cachexia (HR 1.43, 95% CI 1.11 – 1.84) and precachexia (HR 1.30, 95% CI 1.02 – 1.65) were both independently associated with worse overall survival (Table 3). Again, results were similar in multivariable analyses when we adjusted for MELD score, ascites, and encephalopathy rather than Child Pugh class.

DISCUSSION

Although cachexia has been identified as an important prognostic factor in several cancers, data are limited on its prevalence and clinical significance in HCC. In this study using clinically granular data from a large and diverse cohort, we found pre-treatment weight loss is prevalent, with 25% of patients experiencing cachexia and 33% of patients having precachexia. Cachexia and precachexia impacted patients across the spectrum of cirrhosis severity and HCC tumor stages, including some with compensated cirrhosis and early-stage tumors. Notably, 43% of patients with cachexia had BCLC stage 0/A tumors. Patients with cachexia were less likely to receive HCC treatment and had significantly worse survival compared to those without weight loss. Further, patients with precachexia had intermediate survival outcomes compared to those with cachexia and those without significant weight loss. To our knowledge, this is the first study to comprehensively describe the prevalence and clinical outcomes of cancer cachexia in a well characterized cohort of patients with cirrhosis and HCC.

Cachexia is multifactorial and thought to be driven by tumor- and inflammatory-secreted factors. The assessment of cachexia in HCC is particularly challenging as the tumor predominately arises in the background of cirrhosis, a disease which itself leads to muscle wasting (sarcopenia) and physical debility (i.e., frailty) in advanced stages. When assessed solely using weight measurements, cachexia may therefore be underrecognized in patients with decompensated cirrhosis that have developed ascites despite significant loss of muscle mass. Prior studies have evaluated the prognostic role of sarcopenia and body composition in patients with HCC by performing cross-sectional skeletal muscle measurements.[5, 24] However, these studies are limited by one-time measurements, the extrapolation of imaging definitions of sarcopenia based on other cancers, and the difficulty distinguishing HCC-related sarcopenia from that related to the underlying cirrhosis. Alternatively, serum biomarkers are easier to follow longitudinally and may facilitate earlier detection of patients with cachexia.[25, 26]

The constucts of cachexia, malnutrition, and frailty are distinct but overlap in patients with cirrhosis and HCC. While all patients with cachexia are malnourished, not all patients that are malnourished experience cachexia.[27, 28] When we performed subgroup analyses by neutrophil-lymphocyte ratio[29] and Prognostic Nutritional Index (PNI), surrogates for nutritional and immunological status[30], we found cachexia remained associated with worse survival among the subgroups of patients with low PNI and high NLR (Supplemental Table 1). As this was a retrospective study, we did not have data on patient-reported dietary intake and other inflammatory markers. Additionally, patients may have malnutrition and frailty related to the underlying cirrhosis[24, 31], whereas cachexia is a cancer-related phenomenon. The high prevalence of cachexia among patients with Child Pugh class A cirrhosis in our

study suggests cachexia is a distinct process as this population generally has minimal to no cirrhosis-related frailty.[32] Further studies are needed to determine the association between objective measures of frailty (e.g., Liver Frailty Index[33]) and cachexia in patients with HCC.

Most prior clinical studies evaluating cancer cachexia have focused on its prevalence among patients with advanced stage tumors.[16, 34] However, we found cachexia and precachexia were prevalent across all HCC stages, including in patients with early stage tumors. Gannavarapu and colleagues previously demonstrated the survival impact of cachexia and precachexia varied across the spectrum of solid tumor types.[35] Cachexia is highly prevalent in traditionally aggressive cancers (e.g., pancreas, small cell lung cancer) affecting up to 80% of patients; there are fewer data comparing prevalence of cachexia within a cancer type.[36, 37] While HCC is generally considered to be an aggressive cancer, its growth patterns are heterogeneous, with up to 1 in 4 tumors exhibiting indolent behavior.[38, 39] It is possible that the presence of pre-treatment cachexia may be a marker of more aggressive cancer phenotype, regardless of tumor burden, or that more aggressive tumors secrete certain humoral factors that result in significant weight loss.[10]

Notably, we observed that cachexia appeared to play an important role in survival in patients with Child Pugh A cirrhosis, whereas there was no significant difference in survival between the cachexia and non-cachexia groups among those with Child Pugh class C cirrhosis. Patients with more advanced liver disease (i.e., Child Pugh class B or C cirrhosis) have a significant competing risk of mortality that is unrelated to their HCC, as the median overall survival of patients with decompensated cirrhosis is approximately 2 years.[40] This scenario is in stark contrast to patients with compensated (i.e., Child Pugh class A) cirrhosis and HCC, in whom the competing risk of liver-related mortality is significantly lower. This finding is consistent with the idea that the prognostic value of cachexia as a biomarker in HCC is distinct from the concept of physical frailty related to cirrhosis and liver dysfunction itself. These data suggest early recognition of minimal weight loss and appropriate interventions may improve survival.

Management of cancer cachexia is intrinsically complex due to its multifactorial nature, and has traditionally focused on nutritional supplementation, appetite modulators and aggressive treatment of the underlying tumor itself.[41] More recently, preclinical models have identified several promising therapeutic targets (e.g., IL-6, IL-1, TNF-alpha, COX-2, TLRs) and various clinical trials of unimodal and multimodal interventions for cachexia prevention and treatment are ongoing.[42, 43] Early identification of cachexia may lead to better outcomes, as advanced (i.e., refractory) cachexia is considered terminal. This would be of particular importance in patients with HCC given the presence of concomitant cirrhosis, with the goal to begin therapy prior to development of hepatic decompensation.

Though our study has several strengths including its large sample size and well characterized cohort with granular information on degree of liver dysfunction and longitudinal weight assessments, it has a few limitations. First, this was a retrospective cohort study, so there is inherent potential for selection bias and unmeasured confounders. Second, while we used international consensus definition of cachexia, it is based on a dichotomous cutoff of 5% total body weight. Third, in patients with cirrhosis in particular, the presence of

ascites and/or diuretic use may result in measurement bias due to the inaccurate assessment and/or fluctuation of patient weights. However, we are likely *underestimating* the true prevalence of cachexia in our study, as ascites would result in "artificial" weight gain. Further, after we excluded patients with any history of ascites or diuretic use, cachexia was still present in 16.7% of patients, and after we excluded patients with uncontrolled ascites in sensitivity analyses (n=30), results were unchanged (data not shown). Fourth, given the retrospective nature of this study we were unable to evaluate intentional vs unintentional weight loss; however, large fluctuations in weight from intentional weight loss are likely to be uncommon in 6 months prior to HCC diagnosis. We also lacked granular information on patient-reported dietary intake and serum inflammatory markers. Finally, though trends were consistent across various subgroups, our study was underpowered to detect statistically significant differences in survival in some of these smaller groups. However, we believe these limitations are outweighed by the granular clinical data included in our analyses; to our knowledge, this is the first study to adjust for severity liver dysfunction and treatment receipt in survival analyses.

In conclusion, we found 1 in 4 patients with HCC present with cachexia, which appears to be an important prognostic factor in HCC. Given its association with survival, early recognition and treatment of cancer-associated wasting is a potential novel intervention target for reducing mortality in patients with HCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations:

BCLC	Barcelona Clinic Liver Cancer
HR	hazard ratio
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
NAFLD	nonalcoholic fatty liver disease
OR	odds ratio

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What You Need to Know

Background

Cancer cachexia is a wasting syndrome that adversely impacts up to 50% of patients with various types of cancer. Little is known about the prevalence and significance of cachexia in patients with hepatocellular carcinoma (HCC).

Findings

1 in 4 patients with HCC present with cachexia at time of cancer diagnosis, including nearly half of patients with early stage tumors. Compared to patients who did not lose weight, patients with cachexia were less likely to receive HCC treatment and had worse survival.

Implications for Patient Care

Early recognition and treatment of cancer cachexia may lead to improved quality of life and survival in patients with HCC.
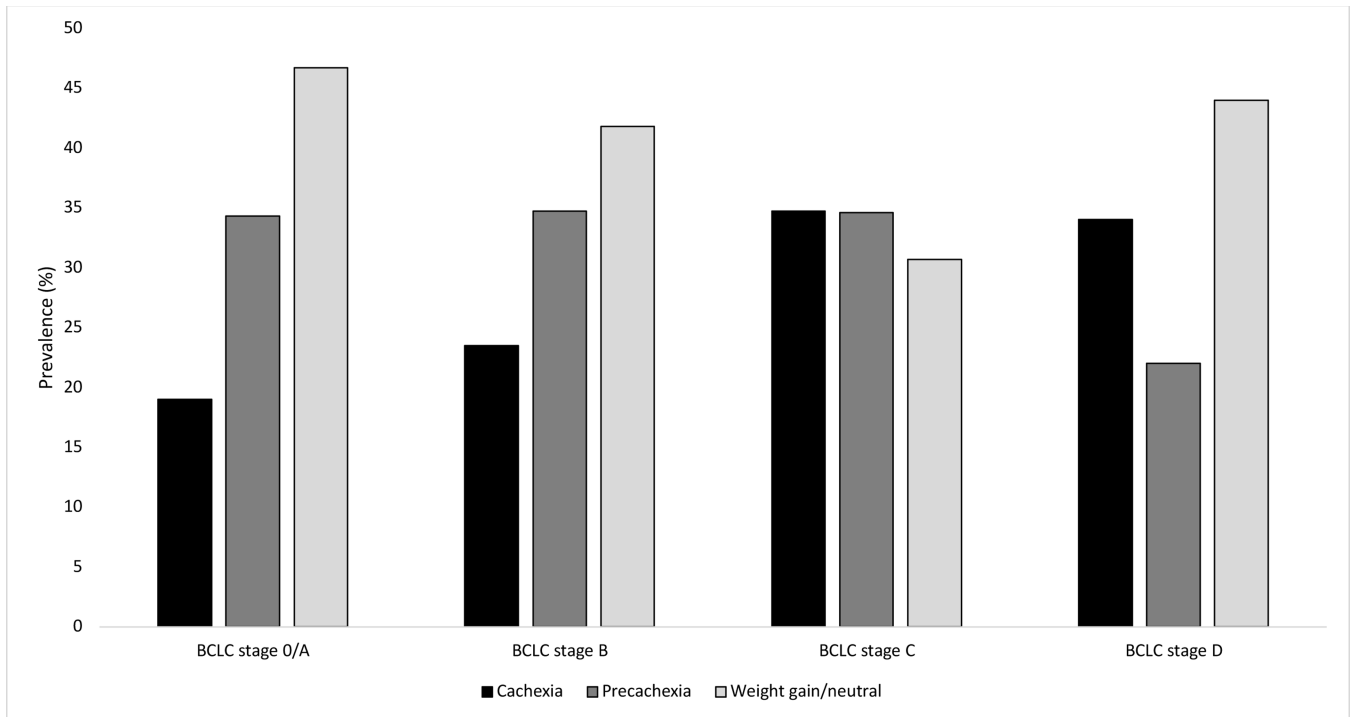
Figure 1.
Prevalence of cachexia and pre-cachexia in patients with HCC, stratified by BCLC tumor stage
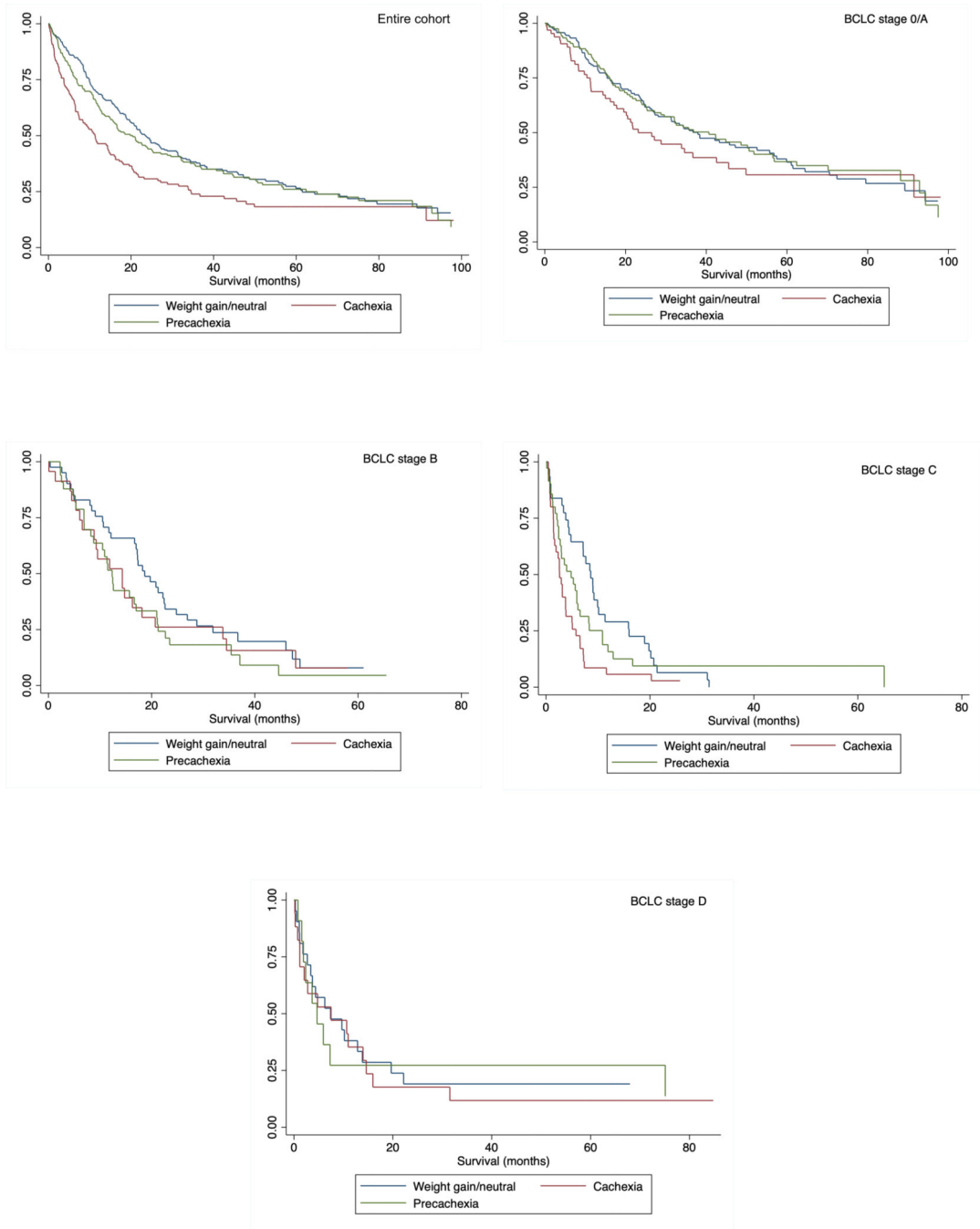
Figure 2.
Overall survival among patients with HCC with cachexia, precachexia, and those who had weight gain/weight neutral in in a) the entire cohort, b) BCLC stage 0/A, c) BCLC stage B, d) BCLC stage C, and e) BCLC stage D HCC
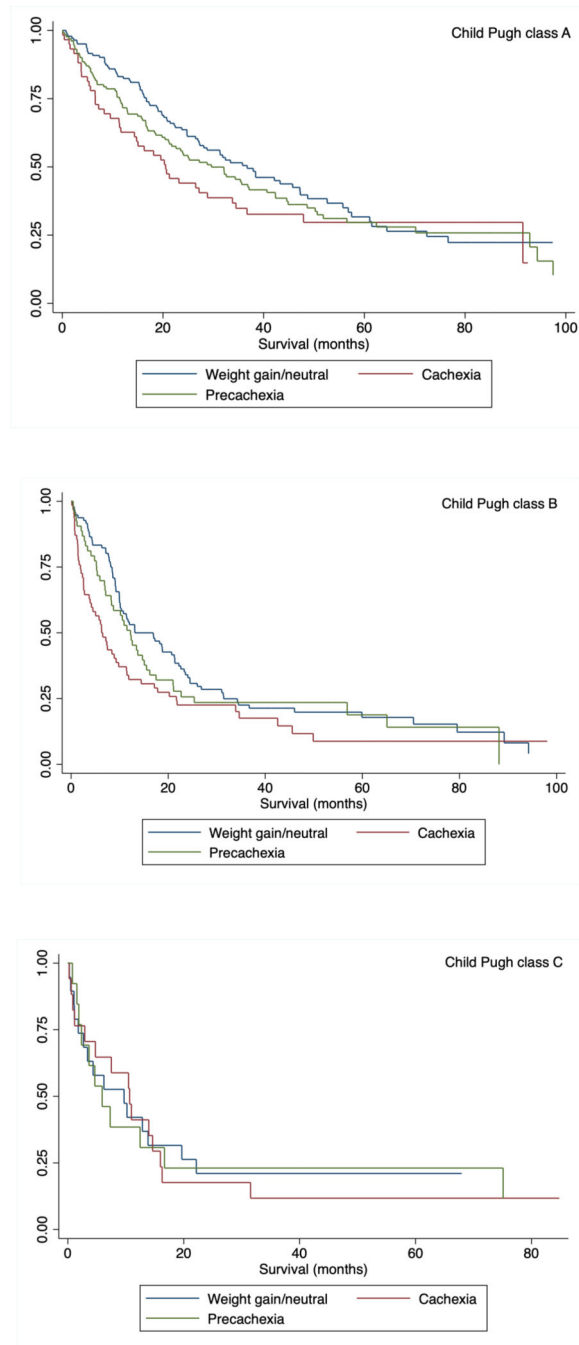
Figure 3.
Overall survival, stratified by presence of cachexia, among patients with HCC and a) Child Pugh class A cirrhosis, b) Child Pugh class B cirrhosis, c) Child Pugh class C cirrhosis

Table 1.

Patient and tumor characteristics of the entire cohort, stratified by presence of cancer cachexia at time of HCC diagnosis (n=604)

| Variable	Cachexia (n=143)	Pre-cachexia (n=201)	Stable weight/weight gain (n=260)	p-value
Age, mean (SD)	60.8 (9.9)	62.0 (8.9)	60.3 (8.6)	0.13
Male sex, n (%)	102 (71.3)	156 (77.6)	178 (68.4)	0.09
Race/ethnicity, n (%)				0.62
White	44 (30.8)	68 (33.8)	82 (31.5)	
Black	49 (34.3)	66 (32.8)	91 (35.0)	
Hispanic	44 (30.8)	59 (29.4)	72 (27.7)	
Asian	3 (2.1)	8 (4.0)	9 (3.5)	
Other	3 (2.1)	0 (0.0)	6 (2.3)	
Body Mass Index (BMI), median (IQR)	25.4 (21.9 – 29.5)	28.3 (24.5 – 32.4)	28.5 (25.4 – 32.9)	<0.001
BMI category				<0.001
< 25 kg/m^2	66 (46.2)	59 (29.5)	49 (18.9)	
25 – 30 kg/m^2	48 (33.6)	71 (35.5)	107 (41.2)	
> 30 kg/m^2	29 (20.3)	70 (35.0)	104 (40.0)	
Hospital site, n (%)				0.54
Parkland	101 (71.1)	140 (69.7)	193 (74.2)	
UT Southwestern	41 (28.9)	61 (30.4)	67 (25.8)	
Insurance status, n (%)				0.56
Medicare	24 (16.9)	36 (18.1)	58 (22.4)	
Medicaid	56 (39.4)	73 (36.7)	102 (39.9)	
Other	38 (26.8)	44 (22.1)	59 (22.8)	
Private	15 (10.6)	30 (15.1)	26 (10.0)	
Uninsured	9 (6.3)	16 (8.0)	15 (5.4)	
Liver Disease etiology, n (%)				0.07
HCV	84 (58.7)	131 (65.2)	164 (63.1)	
NAFLD	19 (13.3)	35 (17.4)	31 (11.9)	
Alcohol	23 (16.1)	20 (9.6)	44 (16.9)	
HBV	8 (5.6)	11 (5.5)	16 (6.2)	
Other/unknown	9 (6.3)	3 (1.5)	4 (1.5)	
Cirrhosis, n (%)	136 (95.1)	179 (89.5)	244 (93.9)	0.16
Child Pugh, n (%)				<0.001
A	59 (41.8)	133 (66.8)	145 (55.8)	
B	65 (46.1)	53 (26.6)	96 (36.9)	
C	17 (12.1)	13 (6.5)	19 (7.3)	

Variable	Cachexia (n=143)	Pre-cachexia (n=201)	Stable weight/weight gain (n=260)	p-value
ECOG performance status, n (%)				0.004
0	83 (60.1)	132 (67.4)	172 (67.2)	
1	28 (20.3)	53 (27.0)	58 (22.7)	
2	21 (15.2)	10 (5.1)	23 (9.0)	
3 or 4	6 (4.4)	1 (0.5)	3 (1.2)	
Ascites, n (%)				<0.001
None	61 (42.7)	140 (69.7)	164 (63.1)	
Mild/controlled	71 (49.7)	51 (25.4)	82 (31.5)	
Severe/uncontrolled	11 (7.7)	10 (5.0)	14 (5.4)	
Hepatic encephalopathy, n (%)				0.02
None	100 (69.9)	172 (85.6)	206 (79.2)	
Mild/controlled	39 (27.3)	28 (13.9)	52 (20.0)	
Severe/uncontrolled	3 (2.1)	1 (0.5)	2 (0.8)	
Platelet count (10^9/L), median (IQR)	130 (77 – 184)	125 (82 – 191)	104 (68– 156)	
AFP (ng/mL), median (IQR)	38 (5 – 699)	22 (6 – 166)	16 (5 – 188)	
AFP (ng/mL), n (%)				0.02
<20	65 (45.5)	93 (46.2)	137 (52.7)	
20–200	30 (21.0)	61 (30.4)	73 (28.1)	
>200	48 (33.6)	47 (23.4)	50 (19.2)	
Number of tumors at diagnosis, n (%)				0.53
1	89 (64.0)	117 (58.2)	168 (65.1)	
2	24 (17.3)	39 (19.4)	42 (16.3)	
3 or more	9 (6.5)	24 (11.9)	25 (9.7)	
Infiltrative and/or innumerable	17 (12.2)	21 (10.5)	23 (8.9)	
Largest tumor diameter (cm)				<0.001
<2 cm	20 (14.9)	37 (19.0)	58 (23.1)	
2–5 cm	62 (46.3)	109 (55.9)	148 (59.0)	
>5 cm	52 (38.8)	49 (25.1)	45 (17.9)	
Infiltrative-type tumor, n (%)	22 (16.4)	27 (13.7)	24 (9.5)	0.12
Extrahepatic metastases, n (%)	10 (7.9)	6 (3.0)	8 (3.1)	0.11
BCLC stage at diagnosis				0.007
0/A	67 (47.2)	121 (60.2)	165 (63.7)	
B	23 (16.2)	34 (16.9)	41 (15.8)	
C	35 (24.6)	35 (17.4)	31 (12.0)	
D	17 (12.0)	11 (5.5)	22 (8.49)	
Received any HCC treatment (%)	91 (63.6)	171 (85.1)	221 (85.0)	

Variable	Cachexia (n=143)	Pre-cachexia (n=201)	Stable weight/weight gain (n=260)	p-value
Most definitive HCC treatment				<0.001
Resection	15 (10.6)	48 (23.9)	42 (16.3)	
Ablation	17 (12.1)	32 (15.9)	58 (22.5)	
OLT	14 (9.9)	17 (8.5)	30 (11.6)	
TACE/TARE/SBRT	33 (23.4)	53 (26.4)	79 (30.6)	
Systemic therapy	12 (8.5)	21 (10.5)	12 (4.6)	
None/BSC	50 (35.5)	30 (14.9)	37 (14.3)	

*
<5% missing data for all variables unless otherwise specified

AFP – alpha-fetoprotein, BCLC - Barcelona Clinic Liver Cancer; HBV – hepatitis B virus; HCC - hepatocellular carcinoma; HCV – hepatitis C virus; IQR – Interquartile range; NAFLD – nonalcoholic fatty liver disease; SD – standard deviation

Table 2.

Correlates of pre-treatment cachexia (at time of HCC diagnosis)

Variable	Univariate		Multivariable (n=563)	
	OR	95% CI	aOR	95% CI
Female sex	1.06	0.70 – 1.60	1.15	0.69 – 1.92
Age	1.01	0.99 – 1.03	1.01	0.98 – 1.03
Race/ethnicity				
White	Ref	Ref	Ref	Ref
Black	1.06	0.67 – 1.69	0.75	0.42 – 1.32
Hispanic	1.15	0.71 – 1.85	1.08	0.61 – 1.88
Asian	0.60	0.17 – 2.15	0.41	0.08 – 2.19
Health system				
Safety-net	Ref	Ref		
University	1.06	0.70 – 1.60		
Insurance status				
Medicare	Ref	Ref		
Medicaid	0.80	0.47 – 1.37		
Other/Parkland	1.15	0.71 – 1.86		
Private	0.84	0.44 – 1.59		
None	0.94	0.42 – 2.09		
Liver disease etiology				
HCV	Ref	Ref	Ref	Ref
Alcohol	1.26	0.74 – 2.15	0.86	0.44 – 1.70
NASH	1.01	0.57 – 1.78	0.57	0.27 – 1.21
HBV	1.04	0.46 – 2.38	1.60	0.64 – 4.05
Other	4.51	1.63 – 12.48	4.32	1.41 – 13.24
Liver disease etiology				
Viral	Ref	Ref		
Nonviral	1.28	0.86 – 1.91		
Child Pugh class				
A	Ref	Ref	Ref	Ref
B	2.06	1.37 – 3.08	2.08	1.28 – 3.38
C	2.50	1.30 – 4.80	2.39	1.10 – 5.18
Ascites				
None	Ref	Ref		
Controlled	2.66	1.79 – 3.96		
Uncontrolled	2.28	1.06 – 4.91		

	Univariate		Multivariable (n=563)	
Variable	**OR**	**95% CI**	**aOR**	**95% CI**
Hepatic encephalopathy				
None	Ref	Ref		
Controlled	1.84	1.18 – 2.87		
Uncontrolled	3.78	0.75 – 19.01		
BCLC stage at diagnosis				
0/A	Ref	Ref		
B	1.31	0.76 – 2.24		
C	2.26	1.39 – 3.69		
D	2.20	1.16 – 4.18		
AFP (ng/mL), n (%)				
<20	Ref	Ref	Ref	Ref
20–200	0.79	0.49 – 1.28	0.69	0.40 – 1.19
>200	1.75	1.13 – 2.72	1.14	0.65 – 2.02
Tumor number			1	
1	Ref	Ref	Ref	Ref
2	0.95	0.57 – 1.59	0.83	0.47 – 1.46
3 or more	0.59	0.28 – 1.24	0.43	0.19 – 0.98
TNTC/infiltrative	1.24	0.67 – 2.27	0.45	0.18 – 1.1
Maximum tumor diameter				
<2 cm	Ref	Ref	Ref	Ref
2–5 cm	1.15	0.66 – 2.00	1.23	0.68 – 2.23
>5 cm	2.63	1.46 – 4.74	3.20	1.56 – 6.56
ECOG performance status				
0	Ref	Ref	Ref	Ref
1	0.92	0.57 – 1.49	0.67	0.38 – 1.17
2	2.33	1.28 – 4.24	1.76	0.84 – 3.70
3	5.49	1.52 – 19.92	1.76	0.34 – 9.11

AFP – alpha-fetoprotein; CI – confidence interval; HBV – hepatitis B virus; HCV – hepatitis C virus; NASH – nonalcoholic steatohepatitis; OR – odds ratio, TNTC – too numerous to count

Table 3.

Correlates of overall survival

	Univariate		Multivariable (n=588)	
Variable	**HR**	**95% CI**	**aHR**	**95% CI**
Female sex	0.93	0.75 – 1.15	0.95	0.76 – 1.19
Age	1.01	0.996 – 1.02	1.01	1.00 – 1.02
Race/ethnicity				
White	Ref	Ref	Ref	Ref
Black	1.08	0.86 – 1.36	1.01	0.79 – 1.28
Hispanic	1.01	0.79 – 1.28	0.67	0.52 – 0.87
Asian	0.67	0.37 – 1.21	0.85	0.46 – 1.55
Liver disease etiology				
HCV	Ref	Ref		
Alcohol	1.09	0.83 – 1.43		
NASH	1.13	0.86 – 1.49		
HBV	0.92	0.61 – 1.40		
Other	0.76	0.41 – 1.43		
Child Pugh				
A	Ref	Ref	Ref	Ref
B	1.93	1.58 – 2.35	1.66	1.33 – 2.06
C	2.04	1.45 – 2.85	0.71	0.35 – 1.46
Ascites				
None	Ref	Ref		
Controlled	1.60	1.31 – 1.96		
Uncontrolled	2.07	1.41 – 3.03		
Hepatic encephalopathy				
None	Ref	Ref		
Controlled	1.16	0.92 – 1.46		
Uncontrolled	2.19	0.98 – 4.91		
AFP (ng/mL), n (%)				
<20	Ref	Ref	Ref	Ref
20–200	1.26	1.00 – 1.59	1.29	1.01 – 1.65
>200	2.95	2.35 – 3.71	1.83	1.41 – 2.37
BCLC stage at diagnosis				
0/A	Ref	Ref	Ref	Ref
B	2.29	1.77 – 2.95	1.76	1.34 – 2.31
C	5.98	4.63 – 7.71	3.88	2.75 – 5.47
D	2.47	1.76 – 3.46	2.94	1.43 – 6.03

	Univariate		Multivariable (n=588)	
Variable	**HR**	**95% CI**	**aHR**	**95% CI**
Tumor number				
1	Ref	Ref		
2	1.36	1.06 – 1.76		
3 or more	1.87	1.37 – 2.55		
TNTC/infiltrative	5.04	3.75 – 6.76		
Maximum tumor diameter				
<2 cm	Ref	Ref		
2–5 cm	1.49	1.12 – 1.98		
>5 cm	4.19	3.08 – 5.72		
Most Definitive HCC Treatment				
Surgical	Ref	Ref	Ref	Ref
Locoregional	3.73	2.79 – 5.00	4.10	3.00 – 5.59
Systemic	9.54	6.33 – 14.39	3.59	2.20 – 5.86
None/BSC	17.41	12.48 – 24.29	12.65	8.65 – 18.50
Weight change prior to HCC diagnosis				
None/weight gain	Ref	Ref	Ref	Ref
<5% weight loss	1.10	0.88 – 1.36	1.30	1.02 – 1.65
>5% weight loss	1.56	1.23 – 1.97	1.43	1.11 – 1.84

AFP – alpha-fetoprotein; CI – confidence interval; HBV – hepatitis B virus; HCV – hepatitis C virus; NASH – nonalcoholic steatohepatitis; OR – odds ratio; TNTC – too numerous to count