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Serum Adiponectin is Associated with Worsened Overall Survival in a Prospective Cohort of Hepatocellular Carcinoma Patients

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Abstract

Background—Hepatocellular carcinoma (HCC) is the third leading cause of cancer deaths worldwide. The rise in metabolic syndrome has contributed to this trend. Adipokines such as adiponectin are associated with prognosis in several cancers, but have not been well studied in HCC.

Methods—We prospectively enrolled 140 patients with newly diagnosed or recurrent HCC with Child-Pugh A or B cirrhosis. We examined associations between serum adipokines, clinico-pathological features of HCC, and time to death. We also examined a subset of tumors with available pathology for tissue adiponectin receptor (AR) expression by immunohistochemistry.

Results—Median age of subjects was 62 years; 79% were men, 59% had underlying hepatitis C, and 36% were diabetic. Adiponectin remained a significant predictor of time to death (HR: 1.90; 95% CI: 1.05–3.45, p=0.03) in a multivariable adjusted model that included age, alcohol history, CP class, stage and serum AFP level. Cytoplasmic AR expression (AR-1 and 2) in tumors trended higher in those with higher serum adiponectin levels and in those with diabetes mellitus, but the association was not statistically significant.

Conclusions—In this hypothesis-generating study, we found serum adiponectin level to be an independent predictor of overall survival in a diverse cohort of HCC patients.

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Keywords

cancer biology; Hepatocellular carcinoma

Introduction

The incidence of hepatocellular carcinoma (HCC) has tripled in the United States over the last 30 years. This is thought to be at least partly due to metabolic syndrome, which has the highest population-attributable risk for HCC in the United States [1–3]. Patients with features of metabolic syndrome, including obesity, insulin resistance, and diabetes, also have worsened outcomes from several kinds of cancer, including HCC [4, 5].

We and others have found that features of the metabolic syndrome may contribute to more aggressive tumor phenotypes, both in animal models and in patients. For instance, both diet and genetic obesity have been shown to promote HCC development in mouse models [6]. Prior work by our group also suggests an association between increased body mass index (BMI) and vascular invasion in tumors in patients with HCC [7, 8].

There has been growing interest in the relationship between adipokines, such as adiponectin, and cancer. Adiponectin is a hormone that is usually inversely correlated with body mass index and percent body fat. High levels typically predict lower incidences of several types of solid tumors [9, 10], and better prognosis [11].

In this prospective study of patients with HCC, we examined serum adiponectin, leptin, HOMA-IR (homeostasis model assessment-estimated insulin resistance) levels, and clinico-pathologic features of HCC, to evaluate preliminary relationships between adipokines and HCC outcome.

Expression levels of the two adiponectin receptor forms (adiponectin R1 and R2) have also been associated with both physiological and pathological states including obesity and insulin resistance [12]. Reduced AR expression has been implicated in the pathogenesis of NASH and development of cirrhosis [13, 14], so we also examined a subset of subjects for AR expression in tumor and surrounding tissue.

Methods

Study Population

From 2008–2012, 140 adult patients 18 years and older with newly-diagnosed or recurrent HCC at Columbia University Medical Center were recruited for this prospective study and followed until December 2012. Subjects had histologically proven HCC or met AASLD criteria for HCC diagnosis [15]. We excluded patients who had any previous malignancy within the last five years, those that had undergone liver transplant, and those that had received any systemic cancer therapy. Those with Child Pugh C disease and/or clinically significant ascites were also excluded. The protocol was approved by the Columbia University Institutional Review Board, and all subjects signed written informed consent.

Procedures

Subjects completed an epidemiologic questionnaire and underwent a physical exam including weight, height, waist and hip measurements. Fasting morning blood samples were collected at the time of enrollment. Laboratory analyses included a complete blood count, basic metabolic/hepatic panels, hemoglobinA1c, lipid panel, hepatitis screen, AFP, ferritin, transferrin, ceruloplasmin, alpha-1 antitrypsin phenotype, antinuclear antibody, anti-smooth-muscle antibody, and anti-mitochondrial antibody to define the underlying etiology of HCC.

An additional 30 mL fasting blood sample was collected at the same blood draw for adipokine evaluation. Whole blood, plasma, serum and buffy coat were divided into aliquots and frozen at (−) 70 degrees, then run in batches at the Irving Institute's Biomarker Core at Columbia University. Specimens were de-identified with a unique study number and barcode, and results were forwarded to the study coordinator for entry into a secure database. Laboratory personnel were blinded to study hypotheses and outcomes.

Measures

Our main exposures of interest were serum levels of adipokines. We used a radioimmunoassay to measure baseline levels of leptin (RIA Linko, St Charles, MO, quantification limit 0.5 ng/mL, inter-assay precision 4.6%, intra-assay precision 5%), adiponectin (RIA Millipore, Billerica, MA, quantification limit 1 ng/mL, inter-assay precision 6.9%, intra-assay precision 6.2%) and insulin (RIA Siemens, Deerfield Il, quantification limit 2 ulU/mL, inter-assay precision 5.3%, intra-assay precision 4.3%). HOMA-IR was used as a measure of insulin resistance and was calculated as fasting insulin (mU/L) × plasma glucose (mmol/L)/22.5 [16]. All samples were run in duplicate, and the median value was used. Our primary outcome of interest was time to death from diagnosis. Mortality data were obtained from medical records and confirmed with the National Death Index.

The following covariates were used in the analysis: age (≥ or < median), gender, race/ethnicity, etiology of liver disease (HBV, HCV, alcohol, DM), BMI (Kg/m^2), Child-Pugh class, metastasis (yes/no), BCLC stage, Milan criteria (within/outside), and serum AFP levels (≥ or < median). Those who self-reported alcohol use of more than two standard drinks per day (28 oz) consistently for over a year at any point in their lives were classified as having alcohol-related disease. Diabetes was defined as having a fasting glucose greater or equal to 126 mg/dL, or being on drug therapy for diabetes. NASH was not formally assessed because of difficulties assessing it pathologically in the setting of cirrhosis, and because not all subjects had available pathology for review. Since waist to hip ratio (WHR) has often been shown to better estimate mortality risks due to general and abdominal obesity, we conducted separate analyses assessing WHR (≥ or < median) [17]. Variations in circulating levels of serum adipokines have been shown to play a role in liver fibrogenic processes [18, 19], therefore in an exploratory analysis in a subset of patients (54%) for whom pathology data were available, we also assessed the association between Batts-Ludwig stage of liver fibrosis (I–IV) and serum adipokine levels [20].

Immunohistochemistry

Tissue sections from 17 patients were evaluated for adiponectin R1 and R2 expression by immunohistochemistry. Four groups were selected randomly from cases with available formalin-fixed paraffin-embedded tissue based on low and high levels of serum adiponectin (≥ or < median) and degree of fibrosis assessed by Batts-Ludwig stage. After antigen retrieval in ULTRA Cell Conditioning Solution (Ventana Medical Systems, Tucson, Ariz), slides from all cases were stained on an autostainer (Ventana Benchmark Ultra; Ventana Medical Systems) for AR1 (dilution 1:100, rabbit monoclonal antibody; Abcam, Cambridge, MA) and AR2 (374–386, rabbit polyclonal antibody; dilution 1:100; Phoenix Pharmaceuticals, Burlingame, CA). Slides were examined by a liver pathologist blinded to clinical and laboratory values, who scored the expression levels of adiponectin R1 and R2 in both tumor and surrounding tissue as either positive or negative based on presence or absence of staining.

Statistical Analysis

Descriptive statistics including mean levels and ranges were used to summarize baseline adipokine levels. Associations between serum adiponectin, leptin, HOMA-IR (all as categorical variables using median values as cut-offs) and covariates including etiology and clinico-pathologic variables (all as categorical variables) were analyzed using chi-squared tests.

Our preliminary data showed a 3-fold increased risk of death for those with higher than median adiponectin levels (>12,000 ng/mL) in univariate and multivariate models (adjusted for stage, AFP, age, and Child-Pugh class). Our pilot data suggested a median survival of 290 days for the high adiponectin group, and we conservatively assumed a median survival of 600 days for the lower adiponectin group. We would then have had 83% power to identify a survival difference of about 300 days at p=0.05, with 40 patients in each group using Kaplan-Meier analyses. With a sample size of 140 patients, we planned to adjust for additional covariates, including BMI, etiology of liver disease, age, race/ethnicity, stage, and tumor features.

Kaplan-Meier plots and Cox proportional hazard models were used to determine the association between variables of interest and time to death. We defined cut-offs for low and high levels for our main exposure variables (adiponectin, leptin and HOMA-IR) using quartiles of baseline serum levels. Variables that were clinically relevant and showed statistical significance in univariable analysis were included in the multivariable Cox proportional hazards models. Subjects contributed person-time for survival analyses from the date of enrollment to the date of death/date of censoring. Subjects were censored if they were lost to follow-up or at the end of study period (December 31, 2012). There were no significant differences in baseline adipokine levels for the 18 patients that were lost to follow-up. Further, excluding these participants did not lead to any significant change in the hazard ratios in unadjusted and multivariable adjusted Cox proportional hazard models.

In additional analyses, we examined the relationship between insulin resistance (using HOMA-IR) and adipokine level (as continuous variables) using Pearson correlation

coefficients. Since the ratio of adiponectin to leptin has been used as an index to evaluate insulin resistance [21], we assessed adiponectin-leptin ratio as an independent predictor of survival in patients with HCC. Finally, to further evaluate the predictive value of these markers, we tested for interaction and calculated separate hazard ratios stratified by baseline subject and tumor characteristics using medians as cut-offs to define high and low levels of adiponectin, leptin and HOMA-IR. All tests of statistical significance were two sided, and analyses were done using SAS, Version 9.3 (SAS Institute Inc., Cary, NC).

Results

The median age of study participants was 62 years. 79% were men, 49% were non-Hispanic white, 59% had hepatitis C, and 36% were diabetic. 64% were Child-Pugh class A and 44% were within the Milan criteria at enrollment. Mean (median, and range) baseline serum levels were 14.1 (7.8, 1.6–89.3) ng/mL for leptin, 16540.7 (13,050, 850.0–82,400.0) ng/mL for adiponectin and 5.5 (3.2, 0.35–67.60) for HOMA-IR, respectively. Median follow-up was 8 months and median survival time was 18 months. During the follow-up period, 76% of patients received loco-regional therapy, 19% underwent resection, 15% received sorafenib, and 20% underwent a liver transplant.

Subject and tumor characteristics stratified by low (< median) and high (≥ median) levels of serum leptin, adiponectin and HOMA-IR are summarized in Table 1. High adiponectin levels (≥13,050 ng/mL) were associated with female gender (p=0.003), being hepatitis C positive (p=0.002), and being Child-Pugh class B (p<0.001). High leptin (p=0.003) and HOMA-IR (p=0.03) levels were significantly associated with a higher degree of liver fibrosis. Interestingly, adiponectin level was not significantly associated with liver fibrosis (p=0.29).

In univariable analysis, a serum adiponectin level greater than median were significantly associated with survival (HR: 1.83; 95% CI: 1.05–3.19, p=0.03). Leptin (HR: 0.62; 95% CI: 0.35–1.08, p=0.09) and HOMA-IR (HR: 0.77; 95% CI: 0.44–1.34, p=0.36) were not (Table 2 and Figure 1). Adiponectin remained a significant predictor of time to death (HR: 1.90; 95% CI: 1.05–3.45, p=0.03) in a multivariable adjusted model that included age, alcohol history, CP class, Milan criteria and serum AFP level (Table 3). However, the hazard ratio for adiponectin was attenuated when we replaced Milan with BCLC stage (HR: 1.34; 95% CI: 0.73–2.45, p=0.35) or included surgical treatment (HR: 1.71; 95% CI: 0.93–3.17, p=0.09) in the above model. Surprisingly, history of alcohol intake was a significant predictor of better overall survival in both unadjusted and multivariable-adjusted model. This may be because history of alcohol intake was associated with better prognostic variables like lower stage at baseline.

In additional analyses, the relationship between insulin resistance (using HOMA-IR) and adipokine level (as continuous variables) was examined. A significant positive correlation was found between leptin levels and HOMA-IR (Pearson correlation coefficient (r) =0.49; p<0.001), while correlations between HOMA-IR and adiponectin (r=−0.11; p=0.19) were not significant. Every standard deviation increase in adiponectin-leptin ratio was associated with a hazard ratio of 1.38 (p=0.002). This association remained significant (HR=1.38;

p=0.01) after further adjusting for other predictors including age, alcohol history, Child-Pugh class, BCLC stage and serum AFP levels.

Expression levels of adiponectin R1 or R2 receptors were assessed for 17 tissue sections from subjects containing both tumor and non-neoplastic liver parenchyma (Figure 2). Tumors of patients with higher adiponectin levels were more likely to stain positive for both AR1 (*p*=0.08) and AR2 (*p*=0.15) receptors. Staining was predominantly cytoplasmic. AR1 and AR2 expression did not significantly correlate with degree of fibrosis or other clinical or pathological covariates. In general, no significant staining heterogeneity was noted in individual samples. There were also no significant differences in staining pattern or intensity of the background cirrhotic liver for AR1 or AR2 receptors.

Discussion

In this observational study of 140 HCC patients, we found that serum adiponectin level was independently associated with worsened overall survival even after adjusting for important clinical covariates. In a subset of patients with available pathology, adiponectin receptor staining in tumors trended with peripheral adiponectin levels, although these results were not statistically significant likely due to small sample sizes.

Adiponectin is a protein derived from adipocytes which regulates fat and glucose metabolism.[22] Levels are usually lower in those who are obese and diabetic, and are typically increased in those with hepatic fibrosis. [23] In most studies, adiponectin levels predict a better prognosis in cancer patients. [11, 24–29] In contrast, some studies have reported high adiponectin levels to be associated with poor prognosis or more aggressive pathology. For instance, in gastric cancer patients, increased adiponectin levels were associated with higher tumor grade (P=0.02) and more poorly differentiated tumors. [25] Similarly, in prostate cancer, serum adiponectin levels were found to be higher in locally advanced relative to organ-confined disease. [30]

In hepatocellular carcinoma, relationships between adiponectin levels and clinical features of disease are complex. Cell culture and animal models suggest that adiponectin inhibits leptin-induced proliferation of HCC via blockade of downstream pathways including STAT-3, AKT, and M-TOR. [31] Adiponectin also leads to suppression of liver tumor growth and metastasis in mice by inhibiting angiogenesis. [32] Similarly, in a study of human HCC, low adiponectin levels were associated with worsened histological grade of HCC. [33]

In other human studies, however, adiponectin may reflect increased risk of HCC.[34, 35], [36] Elevated adiponectin expression may also correlate with worsened outcome, as noted by a report from Taiwan which suggested that high cytoplasmic staining of HCC tumors with adiponectin was associated with recurrence and worsened survival, possibly via upregulation of AKT. This finding persisted after controlling for BMI and fasting blood sugar. However, this study did not assess peripheral levels of adiponectin. [37].

The median values seen for adipokines here seemed relatively comparable to some other populations in the literature, including those with chronic liver disease and cases with

pancreatic cancer compared with controls, although our ranges did seem a bit broader. [9] [38]We speculate that this may be due to the significant heterogeneity of our patient population, particularly with respect to tumor stage, nutritional status, and degree of underlying liver dysfunction.

Possible mechanisms that could explain our results include a possible angiogenic role and/or an anti-apoptotic effect of adiponectin, particularly in the setting of high levels of glucose [39–41]. In a study of 609 patients with type II diabetes, higher adiponectin levels were also associated with worsened overall survival. This and other studies showed a high correlation between total and HMW adiponectin, so we chose to present total adiponectin here [42].

Another possible explanation for our results is that adiponectin levels may be increased in cirrhosis, and with increasing stages of fibrosis.[43, 44] Cirrhosis is thought to lead to a state of adiponectin resistance, with downregulation of adiponectin receptors in liver tissue and decreased clearance of adiponectin. [45–48]. However, we did not find a statistically significant association between liver fibrosis and peripheral adiponectin levels. Although higher adiponectin levels were seen in those with CP B disease, adjusting for CP class did not significantly affect adiponectin's association with overall survival.

Adiponectin and adiponectin receptor expression have been shown to be reduced in patients with NASH [13]. Obesity can lead to decreased adiponectin levels as well as downregulation of adiponectin receptors leading to insulin resistance. [49, 50] In contrast, cachexia has been associated with increases in adiponectin, even when controlling for BMI. [51] In the elderly, higher adiponectin levels also correlate with mortality, are associated with frailty, and can be modified by exercise. [52, 53] High adiponectin levels have also been shown to be associated with poor outcomes in patients in the ICU, independent of BMI or markers of inflammation. [54] These results highlight the multiple competing effects regulating adiponectin and AR levels in these patients. Interestingly, in our study, subjects self-reported weights which were generally lower several years prior to diagnosis (data not shown), making cachexia related to illness less likely in our population, since we excluded those with clinically significant ascites.

There are several strengths of our study including its prospective nature, and use of REMARK guidelines as its basis.[55] Limitations include a relatively small sample size, assessment of adiponectin levels at only one time point, and variety of treatments given before and after enrollment. Although this heterogeneity may be considered a weakness, it also suggests the potential broad applicability of adiponectin as a prognostic biomarker.

Based on our results, we believe that adiponectin deserves further validation as a simple and practical biomarker to assess outcomes in patients with HCC, particularly in those with features of the metabolic syndrome. There are multiple variables which could have opposing effects on adiponectin levels, including metabolic syndrome, cirrhosis, cachexia, and frailty; separating these out in individual patients and clarifying mechanisms for these associations need further examination. Modulation of adiponectin pathways in those with elevated levels of adiponectin as a potential mechanism to alter disease course (potentially via AKT pathway modulation) also deserves further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Impact

Understanding how adipokines affect HCC outcome may help develop novel treatment and prevention strategies.

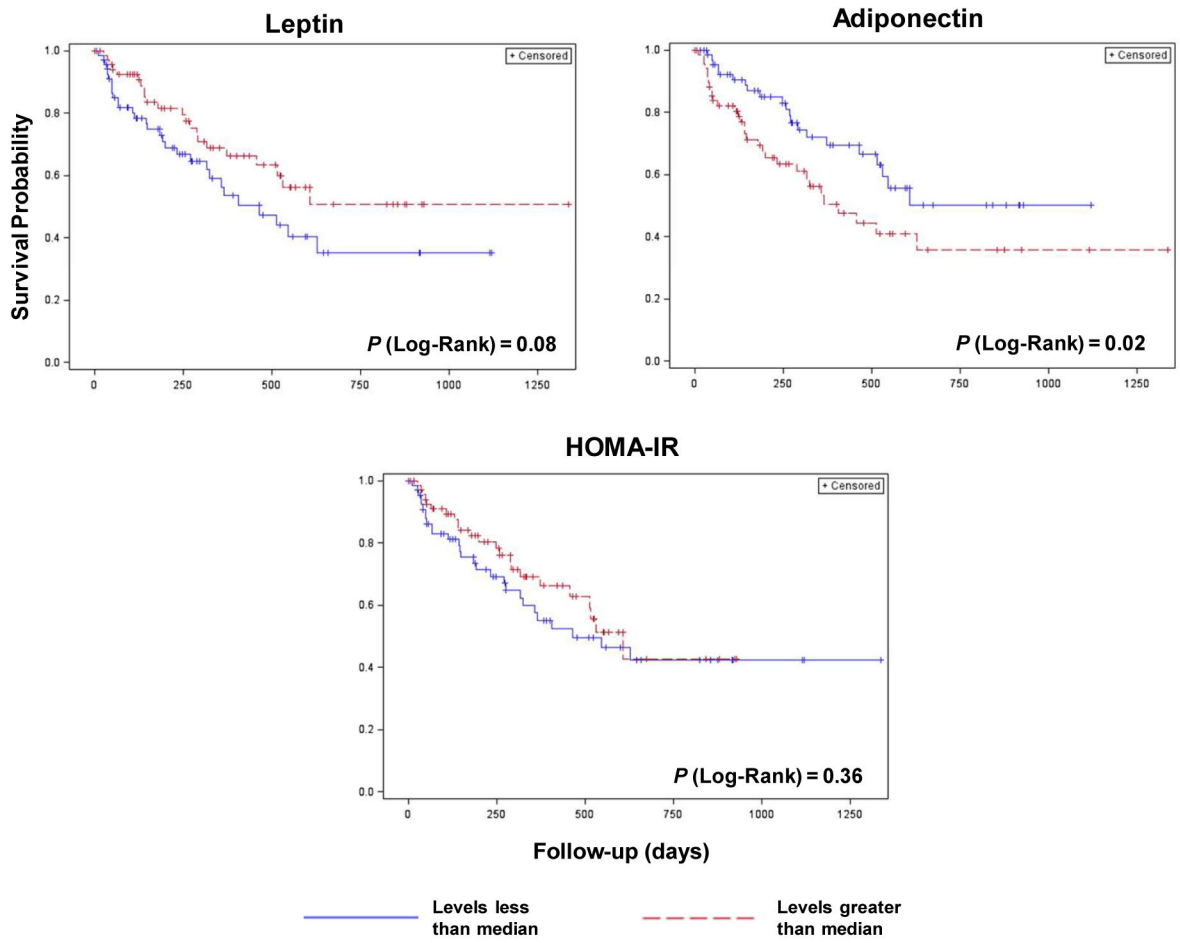

Figure 1.
Kaplan-Meier Plots for Time to Death

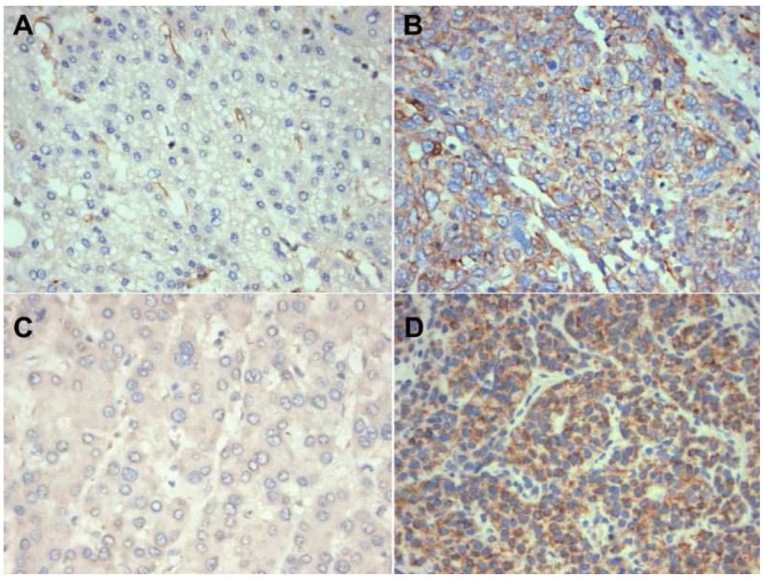

Figure 2.

Adiponectin R1 and R2 expression in HCC by immunohistochemistry. Panels A and C show cases with negative adiponectin R1 and R2 reactivity. In comparison, panels B and D demonstrate strong staining for adiponectin R1 and R2, respectively.

Table 1

Subject and Tumor Characteristics According to Low (<Median) and High (≥Median) Levels of Serum Leptin, Adiponectin and HOMA-IR.

	Missing n (%)	Leptin (ng/mL) (n=140)			Adiponectin (ng/mL) (n=140)			HOMA-IR (n=139)		
Variable		**<7.9**	**≥7.9**	***P*-value**	**<13,050**	**≥13,050**	***P*-value**	**<3.2**	**≥3.2**	***P*-value**
Age	0 (0%)			0.85			0.23			0.44
≥ 62.0		35 (50%)	36 (51%)		32 (46%)	39 (56%)		32 (46%)	37 (53%)	
< 62.0		35 (50%)	34 (49%)		38 (54%)	31 (44%)		37 (54%)	33 (47%)	
Gender	0 (0%)			**0.01**			**0.003**			0.27
Male		61 (87%)	49 (70%)		62 (89%)	48 (69%)		52 (75%)	58 (83%)	
Female		9 (13%)	21 (30%)		8 (11%)	22 (31%)		17 (25%)	12 (17%)	
Hepatitis B virus	0 (0%)			0.24			**0.02**			0.45
Positive		13 (19%)	8 (11%)		16 (23%)	5 (7%)		12 (17%)	9 (13%)	
Negative		57 (81%)	62 (89%)		54 (77%0	65 (93%)		57 (83%)	61 (87%)	
Hepatitis C virus	0 (0%)			0.17			**0.002**			0.33
Positive		45 (64%)	37 (53%)		32 (46%)	50 (71%)		43 (62%)	38 (54%)	
Negative		25 (36%)	33 (47%)		38 (54%)	20 (29%)		26 (38%)	32 (46%)	
Diabetes mellitus	0 (0%)			**0.01**			0.29			**<0.001**
Positive		18 (26%)	32 (46%)		28 (40%)	22 (31%)		13 (19%)	37 (53%)	
Negative		52 (74%)	38 (54%)		42 (60%)	48 (69%)		56 (81%)	33 (47%)	
Alcohol history	0 (0%)			1.00			1.00			0.74
Positive		19 (27%)	19 (27%)		19 (27%)	19 (27%)		18 (26%)	20 (29%)	
Negative		51 (73%)	51(73%)		51 (73%)	51(73%)		51 (74%)	50 (71%)	
BMI at enrollment (Kg/m^2)	0 (0%)			**<0.001**			0.80			**0.005**
< 25		33 (47%)	8 (11%)		19 (27%)	22 (31%)		27 (39%)	14 (20%)	
25–30		28 (40%)	29 (41%)		28 (40%)	29 (41%)		29 (42%)	27 (39%)	
≥ 30		9 (12%)	33 (47%)		23 (33%)	19 (27%)		13 (19%)	29 (41%)	
Waist to hip ratio	30 (21%)			0.12			0.25			0.06
≥ 0.95		22 (42%)	33 (57%)		31 (55%)	24 (44%)		22 (41%)	33 (59%)	
< 0.95		30 (58%)	25 (43%)		25 (45%)	30 (56%)		32 (59%)	23 (41%)	

	Missing n (%)	Leptin (ng/mL) (n=140)			Adiponectin (ng/mL) (n=140)			HOMA-IR (n=139)		
Variable		**<7.9**	**≥7.9**	***P*-value**	**<13,050**	**≥13,050**	***P*-value**	**<3.2**	**≥3.2**	***P*-value**
Child-Pugh class				0.25			**<0.001**			0.35
A	3 (2%)	47 (68%)	40 (59%)		58 (83%)	29 (43%)		44 (64%)	42 (60%)	
B		22 (32%)	28 (41%)		12 (17%)	38 (57%)		25 (36%)	26 (37%)	
Metastasis	0 (0%)			0.11			0.28			0.39
Positive		11 (16%)	5 (7%)		6 (9%)	10 (14%)		9 (13%)	6 (9%)	
Negative		59 (84%)	65 (93%)		64 (91%)	60 (86%)		60 (87%)	64 (91%)	
Within Milan criteria	0 (0%)			0.06			0.61			0.81
Positive		25 (36%)	36 (51%)		29 (41%)	32 (46%)		31 (44%)	30 (43%)	
Negative		45 (64%)	34 (49%)		41 (59%)	38 (54%)		38 (55%)	40 (57%)	
BCLC Stage	0 (0%)			0.17			0.73			0.33
0, A		24 (34%)	32 (46%)		27 (39%)	29 (41%)		25 (36%)	31 (44%)	
B, C		46 (66%)	38 (54%)		43 (61%)	41 (59%)		44 (64%)	39 (56%)	
AFP	0 (0%)			0.31			0.73			0.44
≥ 47.9 ng/mL		38 (54%)	32 (46%)		36 (51%)	34 (49%)		37 (54%)	33 (47%)	
< 47.9 ng/mL		32 (46%)	38 (54%)		34 (49%)	36 (51%)		32 (46%)	37 (53%)	
Batts-Ludwig Stage	65 (46%)			**0.003**			0.29			**0.03**
I–III		17 (53%)	9 (21%)		16 (40%)	10 (29%)		17 (47%)	9 (23%)	
IV		15 (47%)	34 (79%)		24 (60%)	25 (71%)		19 (53%)	30 (77%)	

Abbreviations. BMI: Body mass index; BCLC: Barcelona Clinic Liver Cancer; AFP: Alpha-Fetoprotein; HOMA-IR: Homeostasis model of assessment - insulin resistance; HCC: Hepatocellular Carcinoma.

Table 2

Univariable Cox Proportional Hazards Model for Time to Death

Factor		Reference	HR	95% CI	*P*-value
Age (years)	≥ 62.0	< 62.0	0.90	0.52–1.56	0.71
Gender	Male	Female	0.98	0.51–1.88	0.97
Race/ethnicity	Non-Hispanic Black	Non-Hispanic White	0.71	0.27–1.86	0.49
	Hispanic	Non-Hispanic White	0.95	0.48–1.89	0.89
Hepatitis B virus	Positive	Negative	0.62	0.26–1.45	0.27
Hepatitis C virus	Positive	Negative	1.10	0.62–1.95	0.73
BMI at enrollment (Kg/m^2)	≥ 25	< 25	0.69	0.39–1.24	0.22
	≥ 30	< 30	0.70	0.36–1.34	0.28
Waist to hip ratio	≥ 0.95	< 0.95	1.24	0.65–2.37	0.50
Diabetes Mellitus	Positive	Negative	1.47	0.85–2.55	0.17
Alcohol history	Positive	Negative	0.41	0.18–0.91	**0.03**
Child-Pugh class	B	A	1.89	1.08–3.32	**0.03**
Metastasis	Positive	Negative	2.87	1.53–5.40	**0.001**
Within Milan criteria	Negative	Positive	6.62	2.97–14.71	**<0.001**
BCLC stage	B,C	0,A	2.91	1.52–5.55	**0.001**
AFP (ng/mL)	≥ 47.9	< 47.9	2.26	1.27–4.02	**0.005**
Surgery	Yes	No	0.10	0.04–0.28	**<0.001**
Leptin (ng/mL)	≥ 5.2	< 5.2	0.71	0.40–1.27	0.25
	≥ 7.9	< 7.9	0.62	0.35–1.08	0.09
	≥ 19.9	< 19.9	0.65	0.33–1.28	0.22
Adiponectin (ng/mL)	≥ 8450	< 8450	1.84	0.89–3.80	0.09
	≥ 13050	< 13050	1.83	1.05–3.19	**0.03**
	≥ 21075	< 21075	1.72	0.97–3.05	0.06
HOMA-IR	≥ 0.77	< 0.77	0.86	0.45–1.59	0.63
	≥ 3.20	< 3.20	0.77	0.44–1.34	0.36
	≥ 6.41	< 6.41	1.01	0.53–1.90	0.96

Abbreviations, HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; BCLC: Barcelona Clinic Liver Cancer; AFP: Alpha-fetoprotein; HOMA-IR: Homeostasis model of assessment - insulin resistance.

Table 3

Multivariable Cox Proportional Hazards Model for Time to Death

Factor		Reference	HR	95% CI	*P*-value
Age (years)	≥ 62.0	< 62.0	1.16	0.66–2.03	0.62
Alcohol history	Positive	Negative	0.35	0.15–0.84	**0.02**
Child-Pugh class	B	A	2.18	1.28–3.71	**0.004**
Within Milan criteria	Negative	Positive	7.49	3.22–17.41	**<0.001**
AFP (ng/mL)	≥ 47.9	< 47.9	1.14	0.61–2.14	0.68
Adiponectin (ng/mL)	≥ 13050	< 13050	1.90	1.05–3.45	**0.03**

Abbreviations, HR: Hazard ratio; CI: Confidence interval; AFP: Alpha-fetoprotein.