ORIGINAL RESEARCH

Impact of Sarcopenia on Two-Year Mortality in Patients with HCV-Associated Hepatocellular Carcinoma After Radiofrequency Ablation

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Purpose: Radiofrequency ablation (RFA) appears effective for the treatment of hepatocellular carcinoma (HCC). Evaluation of prognostic factors is imperative for patient selection and improving treatment efficacy. This study aimed to assess sarcopenia as a predictor of the outcome of RFA in patients with HCC.

Methods: This prospective study included all patients with HCC on top of HCV-related cirrhosis who underwent RFA and followed up for a minimum of two years. CT scan was used to determine the skeletal muscle index at the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis muscles. Cross-sectional areas were calculated to obtain a lumbar skeletal muscle index (L3-SMI).

Results: A total of 97 patients were enrolled in the study. The L3-SMI was 46.2 ± 12.1 cm^2/m^2. Older age was the only risk factor associated with sarcopenia (p = 0.001). The overall survival at two years for the whole group was 65.2%. Sarcopenia and MELD score were independent predictors of OS at two years with HR of 7.6 (95% CI: 3.1–18.7) and 2.2 (95% CI: 1.0–4.8), respectively. Recurrence-free survival was 84.1% at two years. Recurrence was not affected by all factors, including sarcopenia.

Conclusion: Sarcopenia is a surrogate predictor of overall survival at two years in HCC patients after RFA. Sarcopenia assessment might be an additional prognostic indicator with conventional biomarkers to optimize the selection criteria for receiving RFA for early-stage HCC.

Keywords: sarcopenia, mortality, hepatocellular carcinoma, radiofrequency ablation

Introduction

Worldwide, hepatocellular carcinoma (HCC) is the 7th most common cancer and the 3rd leading cause of cancer-related deaths with an obvious heterogeneous geographical distribution. In Egypt, HCC is the most common cancer in Egyptian males.[1] Many surgical and non-surgical approaches are available for the treatment of HCC. Non-surgical therapy includes local tumor ablation, transarterial embolization, and radiotherapy.[2] Radiofrequency ablation (RFA) appears to be a local curative treatment of small HCC lesions (< 3 cm in diameter).[3] Existing literature reported promising long-term effectiveness of RFA treatment.[4–6] However, the evaluation of prognostic factors is imperative for patient selection and improving treatment efficacy.

Sarcopenia is a progressive and generalized skeletal muscle disease characterized by accelerated loss of muscle mass and function.[7] It has been associated with

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higher mortality among the general population[8,9] and patients with cancer.[8–10] Prevalence of sarcopenia varies widely from 1 to 29% among older people.[11] Risk factors other than age include sex[12] and inflammatory disease.[13] Cancer patients are at risk of losing muscle mass due to anorexia, reduced physical activity, and aggressive treatment modalities.[14,15] So far, sarcopenia's effect on the outcome of RFA as a curative treatment of HCC is poorly investigated.[16]

This study aimed to assess the possible role of sarcopenia in predicting the outcome of radiofrequency ablation in patients with HCC.

Subjects and Methods

This prospective study included a consecutive sample of all patients with HCC who underwent RFA from August 2015 to April 2018. All patients were followed up for a minimum of two years after RFA. All patients gave informed consent for using their clinical, laboratory, and radiological data at the time of the first examination. The study protocol conformed to the Declaration of Helsinki (1975) and was approved by the local institutional review board. All organs were donated voluntarily with written informed consent, and that this was conducted in accordance with the Declaration of Istanbul.

In the current study, we recruited only patient with HCV-induced liver cirrhosis, and excluded patients with cirrhosis due to other etiologies, such as HBV, alcoholic liver diseases. The aim of this was to unify the studied population, as HCV-induced liver cirrhosis is the most prevalent cause of liver cirrhosis and HCC is Egypt.

Cirrhosis, diagnosed either by histology or clinically, was graded according to the Child-Turcotte-Pugh (CTP) classification and Model for End-stage Liver Disease (MELD) scores as liver impairment measures. HCC was diagnosed according to criteria of the American Association for the Study of Liver Disease[17] and staged by abdominal contrast-enhanced dynamic CT scan or gadolinium-enhanced magnetic resonance imaging (MRI). Moreover, each patient underwent a chest X-ray/ CT scan and bone scanning, as requested by the treating physicians.

Radiofrequency ablation was performed if the patient is a candidate for liver-directed procedures and meets the resectability criteria. These are liver-only disease and a single tumor < 4 cm in diameter with a CTP class A or B.

Initial data collection included age, sex, pre-treatment anthropometric features, laboratory findings including serum albumin, creatinine, international normality ratio (INR), complete blood picture, and alpha-fetoprotein (AFP), and dry weight body mass index (BMI). All data were obtained within two weeks before the RFA session. Follow-up ended after two years or upon patients' death.

Image Analysis and Treatment Modality

CT scans were obtained routinely at baseline for tumor staging purposes within two weeks before initiating treatment and used to determine the skeletal muscle index (SMI). A transverse image at the level of L3 was chosen from each scan. Muscles at this level include psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and the rectus abdominis.[18] Obtained images were analyzed with SliceOmatic V 5.0 software (Tomovision, Montreal, Quebec, Canada), enabling specific tissue selection using previously determined Hounsfield units (HU). Skeletal muscle is selected and quantified by thresholds between −29 to +150 HU.[19] These specific thresholds permit skeletal muscle assessment regardless of ascites in patients with cirrhosis, excluding muscular fat infiltration in the selected section. Two trained physicians checked all CT images. Cross-sectional areas were calculated and normalized for height as reported elsewhere[20] to obtain a lumbar skeletal muscle index (L3-SMI).

The MRI imaging data were excluded to avoid methodological heterogeneity. L3-SMI was expressed in cm^2/m^2. L3-SMI was considered to indicate sarcopenia if $\leq 53\ cm^2/m^2$ in males with a BMI ≥ 25 or $\leq 43\ cm^2/m^2$ with a BMI < 25, and $\leq 41\ cm^2/m^2$ in women.[21]

Statistical Analysis

Statistical analysis was done using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was made using independent sample t-test or Mann–Whitney test. Survival analysis was done using Kaplan-Meier method and comparison between two survival curves was done using Log rank test. Multivariate analysis was done using Cox proportional-hazards model for factors affecting survival on univariate analysis. Hazard ratio (HR) with it 95% confidence interval (CI)

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were used for hazard estimation. A p-value < 0.05 was considered significant.

Results

A total of 97 patients were enrolled in the study. Baseline and disease characteristics of the studied group are shown in Table 1, and laboratory findings in Table 2.

The L3-SMI of the whole studied group was 46.2 ±12.1 cm^2/m^2. Sarcopenia was diagnosed in 42 patients (43.3%). Table 3 shows a comparison between the Sarcopenia group (n=42) and those with normal muscle mass (Non-Sarcopenia group, n=55) regarding patients and disease factors. The only associated risk factor was older age in the sarcopenic group (p = 0.001).

During follow-up, 3 cases underwent transarterial chemoembolization, and 2 underwent transarterial radioembolization. Liver transplantation was done for 16 patients. At the end of follow-up, 33 patients died. Causes of death are

shown in Table 4. The cumulative survival proportion at two years for the whole group (n=97) was 65.2%. Table 5 shows factors affecting overall survival. Sarcopenia was the only factor positively associated with worse survival at two-years (36.6% vs 85.5% for non-sarcopenic patients, p < 0.001). MELD score was near significance on univariate analysis (p = 0.053). On multivariate analysis, sarcopenia and MELD score were the only independent predictors of overall survival (Table 6). Sarcopenia carries a nearly 8-fold higher risk of death within 2 years. As a continuous variable, L3-SMI significantly affected overall survival in males, but not in females (Table 7). In males, higher SMI was associated with better survival with a HR of 0.95 (95% CI: 0.91–0.98).

During follow up, 12 patients developed local recurrence. Recurrence-free survival was 84.1% at two years. Table 8 shows the factors associated with recurrence-free survival (RFS). RFS was not affected by all factors, including sarcopenia.

Discussion

The study demonstrated that sarcopenia was a common occurrence in patients with HCC treated by RFA, affecting 43.3% of them. Older age was the only factor associated with a higher frequency of sarcopenia. The overall survival of these patients at two years was 65.2% and recurrence-free survival was 84.1%. Sarcopenia was a surrogate predictor of overall survival at two years with a hazard ratio of 7.6 (95% CI: 3.1–18.8). On the other hand, there was no association between sarcopenia and disease recurrence in this series.

In Egypt, HCC is considered the most challenging health problem. According to recent statistical data, HCC is the most common cancer in Egyptian males.[1] Many studies described a rising incidence of HCC, which could be attributed to better diagnostic and screening programs, increasing incidence of HCV and cirrhosis, and longer life expectancy of cirrhotic patients.[22] Therefore, identifying patients with a high-mortality risk is an essential step to select the most satisfactory treatment for each patient according to his/her prognosis. Great efforts have been made in this respect that developed many prognostic staging systems. However, prognostic factors for HCC remain controversial. Assessment of general performance and nutritional and functional status of HCC patients can improve the predictive yield of existing staging systems.

A recent review found that many factors have been suggested to affect the survival of patients with HCC who

Table 1 Baseline and Clinical Characteristics of the Studied Group (n=97)

	Value
Age (years)	53.4±6.0
Sex (male/female)	72/25
Body mass index (kg/m^2)	26.2±3.3
Diabetes mellitus	22 (22.7%)
Hypertension	31 (32.0%)
Dyslipidemia	19 (19.6%)
Active hepatitis C viral infection	15 (15.4%)
Disease Characteristics	
Tumor diameter (cm)	2.7±0.7
Child-Turcotte-Pugh class (A/B)	64/33
Model for End-stage Liver Disease score	10 (8–15)

Note: Data are expressed as mean±SD, number (%), or median (range).

Table 2 Laboratory Results of the Studied Group (n=97)

	Value
Hemoglobin concentration (gm/dL)	11.2±1.3
White cell count (x10^3/mm^3)	6.3±1.9
Platelet count (x10^3/mm^3)	177±59
Serum Albumin (g/dL)	3.4±0.4
Serum Bilirubin (mg/dL)	1.7±0.3
Alanine aminotransferase (U/L)	49.9±14.3
Aspartate aminotransferase (U/L)	59.4±11.6
International normalized ratio	1.5±0.2
Serum creatinine (mg/dL)	1.1±0.3
Alpha-fetoprotein (ng/mL)	158 (20–432)

Note: Data are expressed as mean±SD, or median (range).

Table 3 Comparison Between Patients with and without Sarcopenia Regarding Possible Risk Factors

	Sarcopenia Group n=42	Non-Sarcopenia Group n=55	p-value
Age (years)	55.6±5.0	51.7±6.2	0.001
Sex (male/female)	28/14	44/11	0.137
Body mass index (kg/m^2)	26.5±3.5	25.9±3.1	0.346
Diabetes mellitus (yes/no)	9/33	13/42	0.797
Hypertension (yes/no)	13/29	18/37	0.853
Dyslipidemia (yes/no)	9/33	10/45	0.690
Disease Characteristics			
Tumor diameter (cm)	2.8±0.8	2.7±0.7	0.687
Child Class (A/B)	27/15	37/18	0.758
MELD score	10 (8–15)	10 (8–13)	0.365
Laboratory results			
Hemoglobin concentration (gm/dL)	11.2±1.2	11.2±1.5	0.993
White cell count (x10^3/mm^3)	6.3±2.2	6.2±1.6	0.855
Platelet count (x10^3/mm^3)	174±61	180±57	0.642
Serum Albumin (g/dL)	3.4±0.3	3.4±0.4	0.841
Serum Bilirubin (mg/dL)	1.6±0.3	1.7±0.4	0.005
Alanine aminotransferase (U/L)	49.1±13.6	50.5±14.8	0.637
Aspartate aminotransferase (U/L)	60.3±12.5	58.8±10.9	0.525
International normalized ratio	1.5±0.2	1.4±0.2	0.258
Serum creatinine (mg/dL)	1.1±0.3	1.1±0.3	0.669
Alpha-fetoprotein (ng/mL)	154 (45–432)	165 (20–301)	0.626

Note: Data are expressed as mean±SD, or median (range).
Abbreviation: MELD, Model for End-stage Liver Disease.

Table 4 Causes of Death in 33 Patients

Cause	Number (%)
Liver cell Failure	9 (27.3%)
Sepsis	9 (27.3%)
Metastases	7 (21.2%)
Hematemesis	4 (12.1%)
Myocardial infarction	2 (6.1%)
Pulmonary embolism	1 (3.0%)
Accident	1 (3.0%)

underwent RFA. These prognostic factors include liver function as CTP class, high serum levels of AFP, and the presence of portosystemic collaterals.[23] In the current study, we investigated the prognostic significance of sarcopenia in patients with early-stage HCC treated with RFA. All patients in the present study developed HCC on top of HCV-associated cirrhosis. This particular group is impressive because chronic liver diseases are considered a risk factor for sarcopenia.[24] A recent systematic review of 13 studies including 3111 patients indicated a significant association between sarcopenia and all-cause mortality with a pooled adjusted hazard ratio of 1.95 (95% CI: 1.60–2.37).[25] Comparable to the present study, most studies did not find an association between sarcopenia and HCC recurrence.[25]

Sarcopenia has gained increasing interest as a preoperative prognostic indicator in many cancer types.[21,26,27] Previous studies identified sarcopenia as a predictor of poor survival of HCC patients undergoing liver resection.[28–31] However, few studies investigated the impact of sarcopenia on the outcome of RFA. One study included patients subjected to RFA (n=29) or surgical resection (n=61). The authors reported impaired overall survival in sarcopenic patients with no difference between resection and RFA. The presence of sarcopenia did not affect recurrence.[32] Another study said that low pre-treatment muscle mass was an independent predictor for survival. They evaluated muscle mass using the psoas muscle index (PMI, cm^2/m^2) on CT images.[33] Yeh et al studied the prognostic role of pre-sarcopenia in patients treated with RFA. They defined pre-sarcopenia as psoas muscle area index < 4.24 and 2.50 cm^2/m^2 for males and females, respectively. The authors concluded that pre-sarcopenia is the prognostic factor of overall survival, but not of recurrence in early-stage HCC patients undergoing RFA.[34]

Table 5 Factors Associated with Overall Survival at 2 Years in the Studied Group

		n	Events	Cumulative Survival Proportion (%)	p-value
Sarcopenia	Yes	42	25	36.6	< 0.001
	No	55	8	85.5	
Age (years)	> 50	66	24	62.0	0.473
	≤ 50	31	9	71.0	
Recurrence	Yes	12	7	41.7	0.122
	No	85	26	68.6	
Sex	Male	72	23	67.0	0.599
	Female	25	10	60.0	
Diabetes mellitus	Yes	22	6	72.7	0.432
	No	75	27	62.7	
Tumor size (cm)	> 2	79	28	63.7	0.536
	≤ 2	18	5	72.2	
Child Class	A	64	22	64.5	0.995
	B	33	11	66.7	
MELD score	> 9	56	15	72.0	0.053
	≤ 9	41	18	65.1	
Transplantation	Yes	16	4	60.9	0.419
	No	81	29	64.2	
ALBI Grade	G1	66	21	68.2	0.474
	G2	31	12	59.6	
S. Creatinine (mg/dL)	> 1.2	20	4	80.0	0.158
	≤ 1.2	77	29	61.4	
Hemoglobin (gm/dL)	< 12	69	24	64.2	0.748
	≥ 12	28	9	67.9	
ALT (U/L)	> 55	29	8	72.2	0.329
	≤ 55	68	25	62.0	
AST (U/L)	> 40	92	31	65.4	0.756
	≤ 40	5	2	60.0	
INR	> 1.1	93	31	65.8	0.369
	≤ 1.1	4	2	50.0	

Abbreviations: MELD, Model for End-stage Liver Disease; ALBI, albumin-bilirubin grade; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.

In the current study, 43.3% of the patients had sarcopenia. Previous studies have reported a widely variable frequency of sarcopenia in patients with HCC ranging from 12.4% to 66.3%.[25] The only factor positively associated with sarcopenia was older age. However, the study sample was relatively younger than that reported in studies investigating the link between sarcopenia and RFA outcome. For example, 78% of patients in Yuri's study[33]

Table 6 Multivariate Cox Proportional Hazards Model for Factors Affecting Overall Survival

	B	p-value	HR	95% CI for HR	
				Lower	Upper
Sarcopenia	2.026	<0.001	7.59	3.07	18.77
MELD score > 9	0.800	0.040	2.23	1.04	4.78
Child Score B vs A	0.116	0.783	1.12	0.49	2.56
Age > 50 years	0.585	0.201	1.79	0.73	4.40
Size > 2 cm	0.210	0.673	1.23	0.47	3.26
ALBI G2 vs G1	0.533	0.183	1.70	0.78	3.74

Abbreviations: B, regression coefficient; HR, hazard ratio; CI, confidence interval; MELD, Model for End-stage Liver Disease; ALBI, albumin-bilirubin grade.

Table 7 Cox Proportional Hazards Model for Overall Survival and L3-SMI in Males and Females

L3-SMI	B	p-value	HR	95.0% CI for HR	
				Lower	Upper
Males	−0.053	0.005	0.95	0.91	0.98
Females	−0.052	0.118	0.95	0.89	1.01

Abbreviations: B, regression coefficient; HR, hazard ratio; CI, confidence interval; SMI, skeletal muscle index.

were > 60 years, compared to only 9% in the current study. The mean age in Yeh's study[34] was 63.4±10.1 years, while in the present study, it was 53.4±6.0 years. The younger age in the current study supports the concept that sarcopenia is an independent predictor of poor survival, even in younger patients. The young age also indicates the importance of chronic liver disease in the development of sarcopenia. It was reported to affect 30% to 70% of patients with cirrhosis.[24]

The pathogenesis of sarcopenia in cirrhosis is poorly explained, but suggested mechanisms have been proposed indicating an imbalance between muscle breakdown and formation. It is proposed to be affected by protein catabolism and hormonal and metabolic alteration leading to muscle depletion.[24,35] These factors may predispose to poor survival in patients with HCC.[36] Another mechanism may involve decreased insulin-like growth factor-1 (IGF-1), strongly associated with low muscle mass and strength.[37] It has been reported that low plasma IGF-1 in HCC patients is associated with poor overall survival.[38] Sarcopenia was also linked to the tumor necrosis factor-α system, which may enhance tumor migration and invasion in HCC.[39]

Many methods are available for the evaluation of skeletal muscle mass. These include dual-energy X-ray absorptiometry and bioelectrical impedance analysis.

Table 8 Factors Associated with Recurrence-Free Survival at Two Years in the Studied Group

		n	Events	Cumulative Survival Proportion (%)	p-value
Sarcopenia	Yes No	42 55	6 6	76.5 88.0	0.176
Age (years)	> 50 ≤ 50	66 31	8 4	83.9 84.7	0.984
Sex	Male Female	72 25	10 2	82.4 89.2	0.461
Diabetes mellitus	Yes No	22 75	4 8	77.8 86.3	0.453
Child Class	A B	64 33	10 2	81.0 90.7	0.214
MELD score	> 9 ≤ 9	56 41	6 6	86.8 80.9	0.341
ALBI Grade	G1 G2	66 31	9 3	82.9 87.0	0.624
S. Creatinine (mg/dL)	> 1.2 ≤ 1.2	20 77	3 9	83.0 84.6	0.853
Hemoglobin (gm/dL)	< 12 ≥ 12	69 28	7 5	86.9 77.9	0.382
ALT (U/L)	> 55 ≤ 55	29 68	5 7	78.8 87.0	0.481
AST (U/L)	> 40 ≤ 40	92 5	12 0	83.4 100.0	0.434
INR	> 1.1 ≤ 1.1	93 4	12 0	83.6 100.0	0.520

Abbreviations: MELD, Model for End-stage Liver Disease; ALBI, albumin-bilirubin grade; Hb, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.

Currently, CT is considered the gold standard for sarcopenia evaluation owing to its accuracy and wide availability.[40] Different CT methods are used to measure muscle mass. Like the present study, many investigators quantified sarcopenia by measuring muscle mass at the level of L3 vertebra on 2D planar sections of CT scans. This method has been recognized as the most accurate predictor of whole-body muscle mass[41] and is accepted as a marker of sarcopenia and cachexia.[42] Previous studies also showed a good correlation between total muscle area and psoas muscle area at the middle of the third lumbar vertebra level.[43]

In this series, the overall survival at two years was about 65.2%. This figure is a bit lower than some previous studies.[44–46] This may be attributed to inclusion of post-HVC induced cirrhotic cases only in the current study. The most common causes of death were liver failure and sepsis (n=9, 27.3% for both), followed by metastases (21.2%)

There are some limitations to our study. First, we did not measure muscle strength or physical function in our patients. However, muscle mass loss is potentially associated with muscle strength decline. Studies are needed to incorporate muscle power or functional status, which would be as important as muscle mass for defining sarcopenia. Secondly, the follow-up period was relatively short and the sample size was quite small. HCV cirrhosis in many Egyptian patients is well known to be associated with a previous history of nosocomial HCV infection from parenteral mass treatment for schistosomiasis, a disease that is commonly associated with muscle wasting. Further studies should put this point into consideration in addition to the effect of treatment.

In conclusion, sarcopenia assessment might be an additional prognostic indicator with conventional biomarkers to optimize the selection criteria for receiving RFA for early-stage HCC. Future studies with a larger sample size and longer follow-up are vital to confirm the prognostic significance of sarcopenia in HCC patients receiving different treatment modalities.

Disclosure

The authors report no conflicts of interest in this work.

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