Research Article

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Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma

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Background & Aims: Obesity defined by body mass index (BMI) significantly increases the risk of hepatocellular carcinoma (HCC). In contrast, not only obesity but also underweight is associated with poor prognosis in patients with HCC. Differences in body composition rather than BMI were suggested to be true determinants of prognosis. However, this hypothesis has not been demonstrated conclusively.

Methods: We measured skeletal muscle index (SMI), mean muscle attenuation (MA), visceral adipose tissue index, subcutaneous adipose tissue index, and visceral to subcutaneous adipose tissue area ratios (VSR) via computed tomography in a large-scale retrospective cohort of 1257 patients with different stages of HCC, and comprehensively analyzed the impact of body composition on the prognoses.

Results: Among five body composition components, low SMI (called sarcopenia), low MA (called intramuscular fat [IMF] deposition), and high VSR (called visceral adiposity) were significantly associated with mortality, independently of cancer stage or Child-Pugh class. A multivariate analysis revealed that sarcopenia (hazard ratio [HR], 1.52; 95% confidence interval [CI], 1.18–1.96; $p = 0.001$), IMF deposition (HR, 1.34; 95% CI, 1.05–1.71; $p = 0.020$), and visceral adiposity (HR, 1.35; 95% CI, 1.09–1.66; $p = 0.005$) but not BMI were significant predictors of survival. The prevalence of poor prognostic body composition components was significantly higher in underweight and obese patients than in normal weight patients.

Conclusions: Sarcopenia, IMF deposition, and visceral adiposity independently predict mortality in patients with HCC. Body composition rather than BMI is a major determinant of prognosis in patients with HCC.

Keywords: Hepatocellular carcinoma; Body composition; Prognosis; Body mass index.

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Abbreviations: HCC, hepatocellular carcinoma; BMI, body mass index; IMF, intramuscular fat; CT, computed tomography; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; L3, the third lumber vertebra; HU, Hounsfield units; SMI, skeletal muscle index; SATI, subcutaneous adipose tissue index; VATI, visceral adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio; MA, muscle attenuation; HR, hazard ratio; CI, confidence interval; IL-6, interleukin-6; FFA, free fatty acid.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most frequently diagnosed cancer and the third most frequent cause of cancer-related death [1]. Recent epidemiological studies have resulted in the wide recognition of obesity as a significant risk factor for HCC development [2]. We found previously that underweight patients with a BMI <18.5 kg/m^2 have the lowest risk among patients with chronic hepatitis C [3]. However, we recently conducted a nationwide survey to explore the association between BMI and mortality in patients with non-viral HCC, and unexpectedly identified not only obesity but also underweight status as a risk factor predicting poor survival [4]. Such a paradoxical relationship of underweight (high mortality despite low susceptibility) has also been found in patients with coronary heart disease [5], diabetes [6], and renal cell carcinoma [7], and our study was the first to show in patients with HCC. One possible explanation for such a relationship is that underweight patient groups may include those with more advanced disease. However, the observed trend remained after adjusting for significant factors, such as tumor stage and liver functional status, indicating that underweight patients exhibit other key features associated with a poor prognosis.

BMI is a simple anthropometric index based on individual weight and height and is widely used. However, such simplicity

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comes with a cost. BMI is limited anthropometrically, in that it does not assess individual components of body weight such as regional fat distribution or muscle volume. Regional fat distribution plays a crucial role in patients with metabolic syndrome [8]. In fact, we previously reported that visceral fat accumulation, rather than BMI, is an independent risk factor for recurrence of HCC in patients with non-viral disease [9]. Furthermore, loss of skeletal muscle, called sarcopenia, is associated with poor prognoses of several cancers including HCC [10,11]. Sarcopenia may be linked to a poor prognosis not only pathophysiologically by inducing insulin resistance, but also indirectly, by reducing activities associated with daily living [12]. Based on such findings, Ahima *et al.* proposed a new hypothesis that differences in body composition rather than BMI may be true determinants of prognosis [13]. However, most previous studies investigated only the impacts of single body composition components on prognosis [14]; thus, this hypothesis has not been proven conclusively.

In the present study, we explored BMI, skeletal muscle area, intramuscular fat (IMF) deposition, abdominal adipose tissue area and adipose tissue distribution in a large-scale retrospective cohort of 1257 patients with different stages of HCC and comprehensively analyzed the impact of body composition on the prognoses of such patients.

Patients and methods

This study was conducted according to ethical guidelines relevant to epidemiological research promulgated by the Japanese Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor, and Welfare. The study design was described in a comprehensive protocol prepared by the Department of Gastroenterology, the University of Tokyo Hospital and was approved by the University of Tokyo Medical Research Center Ethics Committee (approval number 2058).

Patients

Using a prospective computerized database, we analyzed information on patients diagnosed with HCC at the Department of Gastroenterology, the University of Tokyo Hospital, a tertiary center, from January 2004 to December 2009. We excluded patients with poorly controlled ascites, because this might lead to overestimation of BMI. We included patients with undetected ascites due to diuretic agent usage, since the exclusion of such patients might constitute selection bias. HCC was diagnosed using unenhanced and dynamic computed tomography (CT) [15]. Images were obtained during the early arterial, late arterial, and equilibrium phases, thus at 28, 40, and 120 s after bolus injection of iodinated contrast material. Images were reconstructed at a section thickness of 5 mm and with a reconstruction interval of 5 mm (section thickness 2–2.5 mm, interval 1.5–2 mm, and field of view 24–35 cm for the arterial phase). A diagnosis of HCC was based on typical CT findings: hyperattenuation in the arterial and hypoattenuation in the equilibrium phase [16,17]. We assessed HCC stage using the Barcelona Clinic Liver Cancer (BCLC) staging system [18].

Clinical and anthropometric variables

We recorded the following clinical and anthropometric parameters upon first admission to our department: age; gender; BMI; hepatitis infection status (hepatitis B virus [HBV], hepatitis C virus [HCV], HBV + HCV, or none); daily alcohol consumption ($\leqslant$80 g *vs.* >80 g); smoking status (never, former or current smoker); presence of diabetes; presence of chronic kidney disease defined by estimated glomerular filtration rate <60.0 ml/min/1.73 m^2; history of cardiovascular or cerebrovascular disease; history of lung disease such as asthma and chronic obstructive pulmonary disease; Child-Pugh class; aspartate aminotransferase, alanine transaminase, total bilirubin, and albumin levels; platelet count; BCLC stage; treatment methods for patients with HCC in BCLC 0 or A; history of previous HCC treatment; and alpha-fetoprotein level (<100 *vs.* $\geqslant$100 ng/ml). We also evaluated the body composition parameters described below. We considered the definitions of underweight and obese typically applied to older adults [19] and Japanese populations [20], and we selected the following BMI categories *a priori*: <20.0, underweight; 20.0–24.9, normal; and $\geqslant$25.0, obese. Diabetes was diagnosed based on medical history or a 75-g oral glucose tolerance test [21].

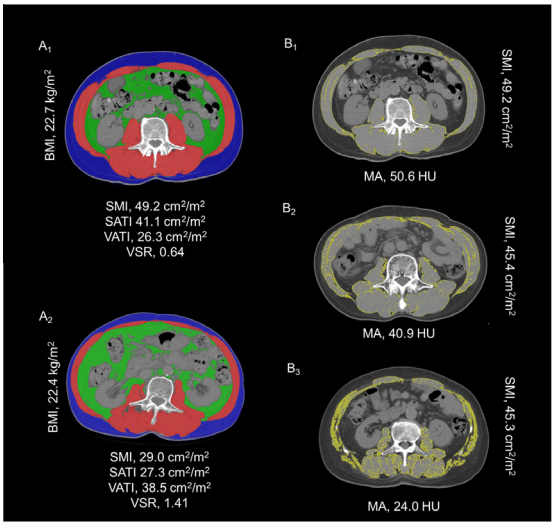

Fig. 1. Cross-sectional computed tomography (CT) images of the third lumbar vertebra used to quantify body composition variables. (A_{1-2}) illustrates the findings of two patients with hepatocellular carcinoma. The BMIs of the two patients were almost identical. The red shadows, the green shadows, and the blue shadows show the skeletal muscle areas, the visceral adipose tissue areas, and the subcutaneous adipose tissue areas, respectively. B_{1-3} illustrates the skeletal muscle area in the three patients, which were nearly identical. The yellow shadows indicate muscle attenuation from −29 to 29 HU. BMI, body mass index; SMI, skeletal muscle index; SATI, subcutaneous adipose tissue index; VATI, visceral adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio; MA, muscle attenuation; HU, Hounsfield units.

CT analyses of body composition variables

We quantified the data from a cross-sectional unenhanced CT image (Aquilion 4/16/64, ONE; Toshiba, Tokyo, Japan; LightSpeed Qx/I, LightSpeed Ultra, LightSpeed VCT, Discovery CT 750 HD; GE Healthcare, Milwaukee, WI, USA) taken solely for the purpose of diagnosing and staging HCC, as described below. We evaluated CT scans performed within 1 month before, or soon after, the first admission to our department. The following measurements were validated by the anatomical radiologists.

We analyzed the cross-sectional CT images at the third lumbar vertebra (L3) using Slice-O-Matic software (version 5.0; Tomovision, Montreal, Canada) to determine skeletal muscle and abdominal adipose tissue area. Muscle areas included the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis muscles. Tissue Hounsfield unit (HU) thresholds were employed as follows: −29 to 150 HU for skeletal muscle, −190 to −30 for subcutaneous adipose tissue and −150 to −50 for visceral adipose tissue [22]. As in previous reports, these body composition variables were normalized for height in meters squared and are expressed as cm^2/m^2. We termed the parameters for skeletal muscle, subcutaneous and visceral adipose tissue as skeletal muscle index (SMI), subcutaneous adipose tissue index (SATI), and visceral adipose tissue index (VATI), respectively. We also calculated visceral to subcutaneous adipose tissue area ratios (VSRs) to explore abdominal adipose tissue distributions. In addition, we calculated mean MA using the same CT images to assess skeletal muscle quality. Low MA indicates increased IMF content that contributes to muscle weakness independent of the age-associated loss in muscle mass [10,23]. Representative images used for analyses are shown in Fig. 1.

We evaluated reproducibility by analyzing data from 70 subjects randomly selected from this cohort to test the reliability of body composition determined by CT. Two trained observers (N.F. and R.N.) measured skeletal muscle area, the corresponding muscle mean CT attenuation, and subcutaneous and visceral adipose tissue area to assess inter-observer reproducibility. One observer repeated the measurements at two time points at least 1 month apart to assess intra-observer reproducibility.