Original Article

Preoperative Assessment of Abdominal Adipose Tissue to Predict Microvascular Invasion in Small Hepatocellular Carcinoma

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Abstract

Background and Aims: Microvascular invasion (MVI) affects recurrence after treatment of small hepatocellular carcinoma (sHCC) of ≤3 cm in size. The present study aimed to investigate whether abdominal subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), and intermuscular adipose tissue (IMAT) are associated with MVI in patients with sHCC. ***Methods:*** A total of 124 patients with pathologically-confirmed sHCC diagnosed on surgical resection at the First Hospital Affiliated to Army Military University were recruited and divided into two groups according to MVI classification criteria (i.e., MVI-positive or MVI-negative). The SAT, VAT, and IMAT areas at the lumbar 3 vertebral level were imaged with abdominal computed tomography and measured using ImageJ software. Their association with MVI in sHCC was analyzed. ***Results:*** Of the 124 patients with sHCC, 67 were MVI-positive and 57 were MVI-negative. Univariate analysis revealed a significant difference in the abdominal VAT and SAT between the MVI-positive and MVI-negative groups ($p<0.05$), with an area under the receiver operating characteristic curve of 0.76 and 0.65, respectively. ***Conclusions:*** The results of this study suggest that the areas of abdominal SAT and VAT are of significant clinical value because they can effectively predict the MVI status in patients with sHCC.

Introduction

Small hepatocellular carcinoma (sHCC) is a common subtype of HCC that has a maximum diameter of ≤3 cm. Advances in imaging techniques, especially the advent of magnetic resonance imaging using gadolinium-ethoxybenzyl-diethylenetriamine-pentaacetic acid (Gd-EOB-DTPA), have enabled an increasing number of sHCCs to be detected at an early stage. Although the Chinese guidelines for the diagnosis and treatment of HCC were standardized in 2019,[1] patients continue to experience a high rate of recurrence and/or metastasis after surgery due to the presence of preoperative microvascular invasion (MVI).

As MVI can only be confirmed after surgical resection currently, many studies have aimed to detect the presence of MVI preoperatively using imaging and/or laboratory indices. Imaging features include the number, size, tumor morphology, envelope integrity, abnormal peritumor enhancement in the arterial phase, and peritumor low signal in the hepatobiliary phase.[2–4] Laboratory indices include hepatitis B virus replication, alkaline phosphatase (ALP) level, alpha-fetoprotein (AFP) level, Ki-67-positive cell index, abnormal prothrombin (PIVKA-II), and steroid hormones.[5–10] However, few investigations have addressed whether abdominal fat content is associated with MVI.

Recent studies have shown that abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) are closely associated with the postoperative prognosis of patients with diabetes, heart disease, pancreatitis, stroke, colorectal cancer, and most recently, COVID-19.[11–16] The implication of abdominal fat content in many diseases informed our hypothesis that abdominal VAT, SAT, and inter-
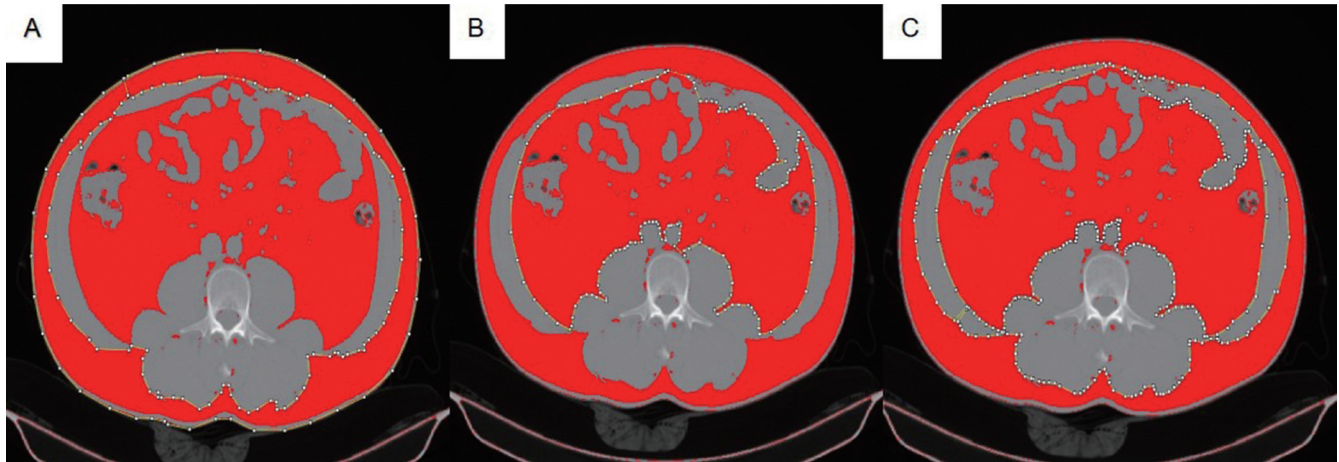
Fig. 1. Illustrations of abdominal fat marked with ImageJ software. SAT (A), VAT (B), and IMAT (C).

muscular adipose tissue (IMAT) may also be associated with MVI in sHCC. This study, therefore, aimed to use fat quantification software to measure the area of abdominal SAT, VAT, and IMAT in patients with sHCC and thus explore the relationship between these metrics and MVI.

Methods

Ethics

This study was approved by the ethics committee of the First Affiliated Hospital of Army Medical University and was conducted in accordance with the principles of the Declaration of Helsinki. Because of the retrospective nature of the study and the use of anonymized patient data, the requirement for individual consent was waived.

Data collection and inclusion/exclusion criteria

The present retrospective case-control study searched the Picture Archiving and Communication System (PACS) for individuals diagnosed with sHCC between July 2017 and July 2019. Patients fulfilling the following criteria were included: complete clinical data, including sex, age, liver function Child-Pugh classification, AFP level (ng/mL), platelet count (10^9/dL), tumor size (cm), etiology of underlying cirrhosis, presence or absence of cirrhosis and treatment of anti-virus regularly, Barcelona Clinic Liver Cancer (BCLC) stage, diagnosis of pathologically-confirmed sHCC after surgical resection, pathological results that clearly marked MVI classifications (M0, M1, M2), and complete and clear computed tomography (CT) images obtained at <2 weeks before surgery. Individuals with incomplete clinical data, a history of other treatments before surgical resection, including radiofrequency therapy, hepatic artery chemoembolization, or liver transplantation, multiple foci (≥2), an interval between the surgery date and CT examination of >2 weeks, or heavy artifacts in CT images were excluded.

CT examination

The CT equipment used at our institution was a dual-source CT scanner (SOMATOM Definition Flash, Siemens, Germa-

ny). It featured a slice thickness and spacing of 5 mm, a scan area that spanned from the top of the diaphragm to the anterior superior iliac spine, a current of 100–750 mA, and a tube voltage of 120 kV. Iohexol contrast agent was administered under high pressure into the forearm via intravenous bolus injection at a dose of 100 mL and a rate of 3.0–3.5 mL/s during the enhancement scan. Images of the arterial, portal, and equilibrium phases were acquired at 40, 70, and 180 s after injection, respectively.

Evaluation methodology

All CT images were assessed by two radiologists with 5 and 10 years of experience in CT diagnosis, respectively. In case of disagreement, consensus was reached through discussion. The central level of the lumbar 3 vertebral body was selected in the PACS system, and the range of fat CT values was set to −190 to −30 Hounsfield units using ImageJ software. The areas of abdominal SAT, VAT, and IMAT at the lumbar 3 vertebral body were outlined and calculated separately in the non-enhanced phase of abdominal CT (Fig. 1), allowing an error of <5% if intestinal contents were mistaken as fat.

Pathological analysis

All pathological examinations were reviewed retrospectively by three experienced pathologists (with 5, 8 and 20 years of experience in liver pathology) who were blinded to the outcomes of the patients. MVI was defined as a tumor within a vascular space lined by endothelium on microscopy. First, MVI status was determined by two younger pathologists. Agreement was reached through consultation in cases of discrepancy. The conclusions of the two pathologists were reviewed by a third pathologist with 20 years of experience.

Statistical methods

Statistical analysis was performed using SPSS (version 24.0; IBM Corp., Armonk, NY, USA). Attribute data conforming to a normal distribution were expressed as ($x \pm s$), and the *t*-test was used for between-group comparisons. Variables with skewed distributions were expressed as the median P_{50} (P_{25}, P_{75}), and between-group comparisons were performed with a stepwise asymptotic method and the non-

Table 1. Clinical characteristics of the patients

Variable	Value
Sex, male:female	101:23
Age in years*	50.0±10.7
Liver cirrhosis	
Present	100
Absent	24
AFP in ng/ mL	36.7 (5.3–192.4)
Child-Pugh	
A	121
B	3
C	0
Tumor size in cm	2.1±0.5
Platelet count as 10^9/dL	126 (95–165)
Etiology of cirrhosis	
HBV	123
HCV	1
BCLC stage	
0	63
A	61
Anti-virus treatment	
Present	48
Absent	76
VAT in mm^2	10,426 (7,042.9–15,926.8)
SAT in mm^2	11,409.2 (7,908.5–16,301)
IMAT in mm^2	247.5 (134.3–419.3)

*Averages.

parametric Mann-Whitney *U*-test. Variables were compared using the χ^2 test. A *p*-value of <0.05 was considered indicative of statistical significance. The area under the receiver operating characteristic (ROC) curve was also calculated.

Results

A total of 124 patients (101 men; mean [±standard deviation] age, 50.1±10.6 years; age range: 23–75 years) were included in the present study. The average size of the lesions was 2.1±0.5 cm (range: 0.8–3 cm). Demographic and clinical data of the patients are summarized in Table 1. Patients were divided into an MVI-negative group (M0 [*n*=57]) and an MVI-positive group (M1 [*n*=54] and M2 [*n*=13]) according to MVI classification. The results were assessed by univariate analysis. Clinical indicators included sex, age, cirrhosis, Child-Pugh classification, AFP level, platelet count, etiology of underlying cirrhosis, presence or absence of cirrhosis, treatment of anti-virus regularly, and BCLC stage. There were no significant differences (*p*>0.05) in these indicators between the MVI-negative and MVI-positive groups (Table 2). Furthermore, although there was no significant difference (*p*=0.421) between the IMAT of MVI-negative (237.8 [126.7, 693.5] mm^2) and MVI-positive group (267.1 [138.9–429.3] mm^2), patients with MVI had larger abdominal VAT areas (13,109.9 [10,213.0, 17,180.6] vs. 7,827.7 [4,894.6, 10,410.5] mm^2,

p<0.001) (Fig. 2) and larger abdominal SAT areas (12,844.0 [9,336.3, 17,641.1] vs. 10,971.9 [5,868.1, 12,709.8] mm^2, *p*=0.003) (Fig. 3) than the MVI-negative group. The areas under the ROC curves for abdominal VAT and SAT were 0.76 and 0.65, respectively (Fig. 4).

In addition, the results of abdominal SAT, VAT, and IMAT between M1 and M2 in the MVI-positive group (Table 3) showed that patients with M2 had more VAT (19,418.3 [1,320.6, 24,601.3] vs. 11,760.5 [8,855.7, 16,276.6] mm^2, *p*<0.001) and more SAT (18,078.3 [13,056.6, 22,121.4 vs. 11,831.2 [8,816.8, 15,890.9] mm^2, *p*=0.003) relative to patients with M1.

Discussion

HCC is the most common primary malignancy of the liver and the sixth most common cancer worldwide, with approximately half of the cases occurring in China.[17,18] With continuous advances in screening technology, an increasing number of sHCCs are detected at an early stage. Once identified, surgical resection, radiofrequency therapy, and liver transplantation remain the most effective treatment methods. However, 60–80% of sHCCs recur after treatment. Petta *et al*.[19] and Cabibbo *et al*.[20] reported that the recurrence rate of HCC following antiviral therapy, such as direct-acting antiviral (DAAs) and interferon (IFN), was lower than when antiviral therapy was not administered. In China, hepatitis B virus (HBV)-related HCC is one of the most common malignant tumors, and patients with HBV usually select DAAs (e.g., entecavir) because of their relative affordability. However, our study showed that there was no statistically significant difference based on whether or not regular antiviral treatment was performed between MVI-positive and MVI-negative groups. In addition, the reason for recurrence can be attributed to the presence of preoperative MVI,[21] which is related to tumor-induced neovascularization, proliferation, and inhibition of apoptosis. Degradation of the basement membrane and protrusion of tumor cells into the capillary lumen are key steps in the formation of MVI.[22]

A previous study demonstrated that obesity may increase the risk of HCC recurrence;[23] however, the body mass index used in that study did not accurately distinguish between abdominal VAT and SAT. Abdominal VAT and SAT levels better reflect the body's fat distribution and are significantly and positively correlated with obesity. Increased SAT density has been reported to be negatively correlated with survival in HCC patients,[24] and a positive correlation between VAT and HCC MVI has also been reported.[23] However, the aforementioned studies obtained samples from tumors of various sizes. The present study specifically selected sHCC because it is a tumor with a relatively high cure rate;[25,26] if the MVI status can be accurately assessed before surgery, the post-operative long-term survival of patients is significantly improved. Hence, establishing a reliable method for ascertaining MVI status preoperatively would be of significant clinical utility. Second, determining MVI status and/or abdominal fat content in larger tumors could be complicated by many uncontrollable factors.[21,27]

The present study evaluated the association between abdominal VAT, SAT, IMAT, and MVI in patients with sHCC. The univariate analysis revealed significant differences in the VAT and SAT between MVI-positive and MVI-negative groups (*p*<0.05). We further found that the higher the content of abdominal VAT and SAT, the more likely MVI in sHCC was present. However, IMAT was not significantly correlated with MVI. In addition, the area under the ROC curve revealed that abdominal VAT and SAT values of 0.76 and 0.65, respectively, could predict positive MVI status; hence, the VAT content predictive of MVI was higher than the SAT con-

Table 2. Univariate analysis for factors associated with MVI in 124 patients operated for sHCC

Variable	MVI− (*n*=57)	MVI+ (*n*=67)	p
Sex, male:female	43	58	0.112
Age in years*	50.1±11.0	49.8±10.6	0.896
Liver cirrhosis			0.988
Present	46	54	
Absent	11	13	
AFP in ng/mL	42.6 (5.5, 222.4)	35.0 (4.8, 190.7)	0.698
Child-Pugh			1.000
A	56	65	
B	1	2	
Platelet count as 10^9/dL	120.0 (95.0, 167.5)	131.0 (94.0, 165.0)	0.757
Etiology of cirrhosis			1.000
HBV	57	66	
HCV	0	1	
BCLC stage			0.069
0	34	29	
A	23	38	
Anti-virus treatment			0.424
Present	19	27	
Absent	38	40	
VAT in mm^2	7,827.7 (4,894.6, 10,410.5)	13,109.9 (10,213.0, 17,180.6)	<0.001**
SAT in mm^2	10,971.9 (5,868.1, 12,709.8)	12,844.0 (9,336.3, 17,641.1)	0.003**
IMAT in mm^2	237.8 (126.7, 693.5)	267.1 (138.9, 429.3)	0.421

*Averages. **Statistically significant difference in VAT and SAT.
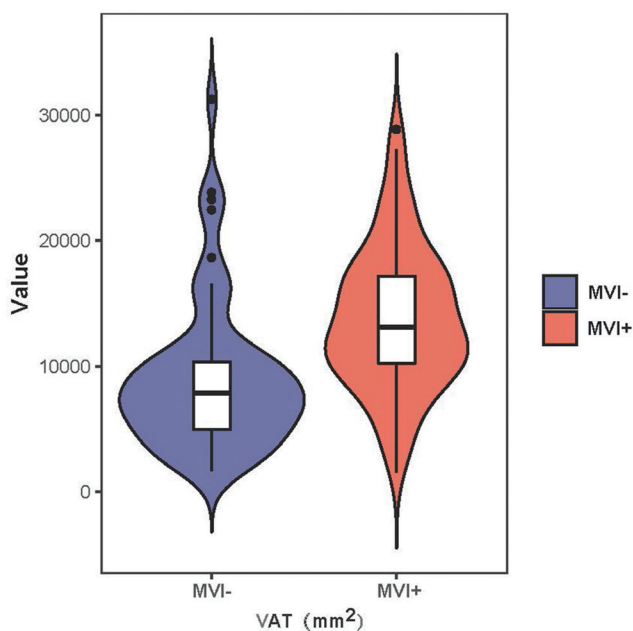

Fig. 2. Comparison of VAT between the MVI-positive and MVI-negative group: the larger the VAT area, the higher the risk of being MVI-positive.
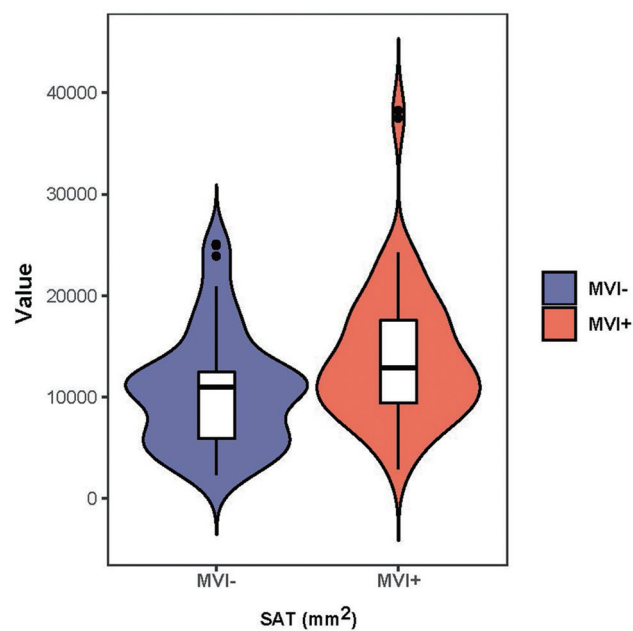

Fig. 3. Comparison of SAT between the MVI-positive and MVI-negative group: the larger the SAT area, the higher the risk of being MVI-positive.
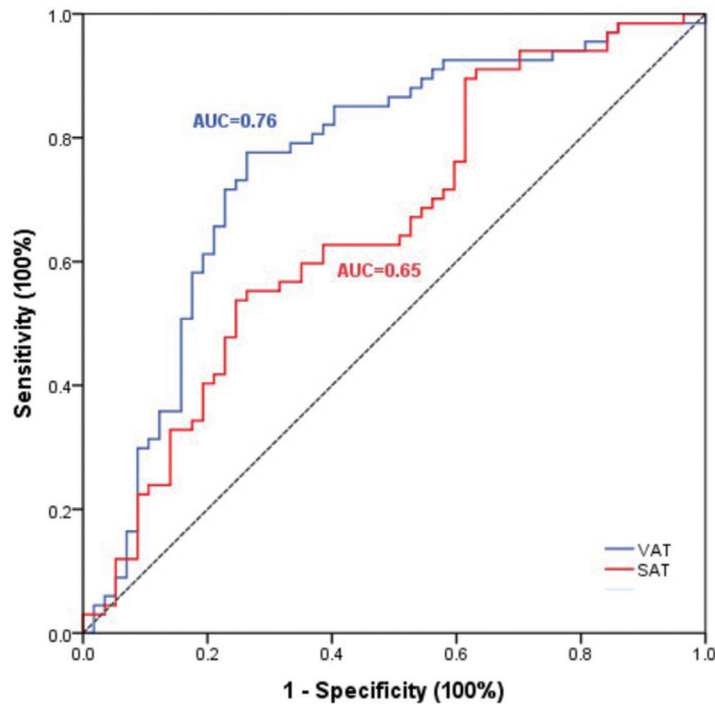
Fig. 4. ROC curve of the VAT and SAT for predicting MVI of sHCC.

tent. Our results also indicated that there was a trend in the M2 subgroup compared to the M1 subgroup; the larger the SAT and VAT areas, the higher the risk of MVI. However, considering our small sample size, more research is needed to verify this conclusion.

The literature on the metabolism of VAT and SAT suggests possible mechanisms that could explain our findings. As an important evaluation indicator of obesity, abdominal VAT is closely related to insulin resistance and negatively affects metabolism and blood glucose levels in patients, thus causing the accumulation of blood glucose in the body.[28] Hyperglycemia increases the structure and size of the microvascular and small vessel basement membrane inside the tumor, causing increased permeability and fragility of blood vessels, as well as the disruption of vascular function that contributes to the formation of MVI in HCC.[29] Furthermore, abdominal VAT can secrete leptin, which reportedly contributes to the development of the proinflammatory state of hepatic stellate cells and the upregulation of provascular endothelial factor.[30,31] This induces neovascularization and further contributes to the development of MVI in HCC. Finally, increases in the abdominal SAT content prompts the secretion of lipocalin and IL-6,[14] as well as the expression of *MCP-1* and *CD68* genes in SAT, in the early stages of cancer.[13] Suggesting that abdominal VAT and SAT play an important role in the recurrence of sHCC, these findings support the validity of our investigation and findings.

The limitations of the present study include its retrospective single-center design, relatively small sample size, and lack of external validation data. Furthermore, since data regarding patient height/weight were incomplete or missing, we could not analyze whether they were correlated with MVI. Additionally, this study only investigated the association between abdominal fat and MVI and did not perform postoperative survival analysis after sHCC surgery. In future studies, we plan to include data from a larger sample for the survival regression analysis. Finally, almost all patients had Child-Pugh A liver function, and this study was thus subject to selection bias. In addition, most patients with Child-Pugh B selected radiofrequency ablation or transcatheter arterial chemoembolization treatment after an adequate explanation by the surgeon. The lesions of such patients were considered unresectable because of the tumor location, patient age, postoperative complications, and economic conditions. In the future, we will include more Child-Pugh B patients for further research.

Conclusions

The presence of MVI in sHCC can be effectively predicted using abdominal VAT and SAT. Our findings suggest, however, that the value of VAT in predicting MVI is higher than that of SAT.

Table 3. Univariate analysis for adipose tissue in M1 and M2 subgroups

Variable	M1 (*n*=54)	M2 (*n*=13)	*p*
VAT in mm^2	11,760.5 (8,855.7, 16,276.6)	19,418.3 (13,240.6, 24,601.3)	0.01*
SAT in mm^2	11,831.2 (8,816.8, 15,890.9)	18,078.3 (13,056.6, 22,121.4)	0.013*
IMAT in mm^2	231.7 (134.7, 411.7)	353.9 (148.7, 634.4)	0.199

*Statistically significant difference in VAT and SAT.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (ZW, HL, XL), acquisition of the data (QX, CJ), analysis and interpretation of the data (CL, HZ, XH), drafting of the manuscript (ZW), critical revision of the manuscript for important intellectual content (PC), and study supervision (KM, LT). All the authors read and approved the final manuscript.

Data sharing statement

The data are available upon reasonable request.

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