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Effect of skeletal muscle index on post-embolization syndrome of hepatocellular carcinoma after transarterial chemoembolization

Xiaojuan Wang[1], Jitao Wang[1,2*], Jinlong Li[1], Kuopeng Liang[1], Shoufang Dai[1], Ruikun Wang[3], Yi Zhang[3], Quan Ren[4], Linglei Meng[1] and Yuzi Qiu[1]

Abstract

Background Skeletal muscle index (SMI) is a commonly used research method for evaluating muscle mass.However, its impact on post-embolization syndrome(PES) of patients with hepatocellular carcinoma (HCC) undergoing transarterial chemoembolization (TACE) is unclear.Our objective was to determine the effect of SMI on PES after TACE in patients with HCC.

Methods We conducted a retrospective analysis of patients who received TACE treatment for HCC at our hospital from 2015 to 2020. The subjects were divided into two groups according to the presence or absence of PES after TACE, and their clinical characteristics were compared.SMI was measured and calculated by cross-sectionally at the level of the third lumbar vertebra based on computed tomography (CT). According to the cutoff value, the patients were classified into either low or high SMI group.Potential risk factors for PES were assessed using univariate and multivariable Cox proportional risk models.

Results A total of 110 people were included in this study, from which including 82 patients experienced PES. Serum albumin was significantly lower in the PES group compared to the non-PES group.The frequency of HCC with a maximum diameter > 3 cm and low SMI in the PES group was significantly higher than in patients without PES. Cox multivariate analysis identified that the maximum diameter of HCC > 3 cm and low SMI were independent predictors of PES after TACE.

Conclusions Low SMI is an independent predictor of PES in HCC patients after TACE treatment, making preoperative CT assessment of skeletal muscle mass is a simple and effective tool for predicting PES.

Keywords Computed tomography, Transarterial chemoembolization, Hepatocellular carcinoma, Skeletal muscle index

*Correspondence:
Jitao Wang
wangjt302@163.com
[1]Hebei Provincial Key Laboratory of Portal Hypertension and Cirrhosis, Xingtai People's Hospital, Xingtai, Hebei 054001, China
[2]Hepatopancreatobiliary Center, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China
[3]Hebei Medical University, Shijiazhuang, Hebei 050017, China
[4]Chengde Medical College, Chengde, Hebei 067000, China

Background

Primary liver cancer is the sixth most frequently diagnosed cancer and the third most prevalent cause of cancer-related death globally [1]. Among individuals under 65 years old, primary liver cancer is the most common tumor-related cause of death in China. Primary liver cancer includes hepatocellular carcinoma (HCC), cholangiocarcinoma, and mixed hepatocellular carcinoma-cholangiocarcinoma, with HCC accounting for 75–85% of cases.Males have a substantially greater incidence and fatality rate than females [2]. China's 2022 guidelines for the diagnosis and treatment of hepatocellular carcinoma state that transarterial chemoembolization(TACE) is a widely used nonoperative treatment for HCC [3]. Postembolization syndrome (PES) is the most common postoperative complication of TACE [4],characterized by nausea, vomiting, right upper quadrant pain, and fever [5, 6]. Due to the inconsistent definition of PES, different studies have disputed the predictors and the value of PES in predicting TACE. In addition, determining the predictive factors of PES is crucial for improving clinical stratification, patient monitoring and avoiding prolonged hospitalization for those with HCC.Previous studies have indicated that tumor burden, no background of cirrhosis and drug-eluting bead TACE (DEB-TACE) are related to the occurrence of PES [7, 8]. However, skeletal muscle index(SMI), which measured by preoperative routine CT with no more extra tests, reflects the nutritional status of the body and is associated with poor prognosis in cirrhosis or HCC [9–13], has yet been used in the prediction analysis of PES.Therefore, this study focused on analyzing the relationship between SMI and PES.

Methods

Study population

A total of 110 HCC patients, consisting of 87 males and 23 females, aged between 34 and 83 years (mean age:61.10±9.35years), who received initial TACE treatment at Xingtai People's Hospital Affiliated to Hebei Medical University from January 2015 to August 2020 were retrospectively included.The body mass index (BMI) of these patients ranged from 16.65 to 38.28 kg/m^2,with an average of 23.45(20.76,25.66)kg/m^2.HCC was diagnosed based on histopathological findings from liver biopsies or radiological features evaluated by dynamic contrast-enhanced computed tomography(CT) or magnetic resonance imaging (MRI) [14]. Inclusion criteria were as follows: (1)HCC patients who could not undergo excision, (2)HCC confirmed by pathology or imaging, (3)HCC patients with Barcelona clinic liver cancer stage A, B or C, (4)Patients with available baseline CT scans, and (5)Patients with complete clinical data.Exclusion criteria included: (1) Child-Pugh class C, (2) Physical status of Eastern Cooperative Oncology Group physical status > 2,(3)Spontaneous rupture of HCC, (4) Presence of other malignant tumors, and(5) Patients with kidney, brain or heart and lung dysfunction.The flowchart of the inclusion was shown in Fig. 1. This study was reviewed and approved by the Ethics Committee of the Institute (2023 [104]) and all patients signed informed forms.

CT scan analysis

CT scans were performed using SOMATOM Definition Flash abdominal CT plain scan, with no more than 7 days between CT and TACE treatment.Thin-layer images between 1 and 1.25 mm obtained through conventional reconstruction were transmitted to the PACS system (Blue Net Technology).Two independent radiologists used ImageJ software to measure the skeletal muscle area in a cross-sectional of the third lumbar vertebra(L3) according to the literature [15]. The area of skeletal muscles, including the psoas, erector, quadratus, transverse abdominis, internal and external oblique and rectus abdominis at the L3 was independently measured, as shown in Fig. 2. The SMI was calculated as the skeletal muscle area divided by the square of the height, with units of cm^2/m^2. According to previous research results, cutoff values for SMI were taken as 44.77 cm^2/m^2 for males and 32.50cm^2/m^2 for females [16], which divided patients into low and high SMI groups.

TACE treatment

TACE was performed by an experienced interventional physician using a large plate digital subtraction angiography system (Philips UNIQ FD20).After completing all preoperative examinations and obtaining voluntarily consent from the patient, the patient was taken to the intervention room for treatment.The patient was positioned supine on the catheter table, and routine disinfection and tissue covering the bilateral groin area were carried out. Then 10 ml of 2% lidocaine in a 1:2 dilution was administered for local anesthesia.The right femoral artery was punctured using the Seldinger method, a 4 F catheter sheath was inserted, and heparin saline was injected to prevent thrombosis.Using a guide wire, the catheter was placed in the superior mesenteric artery, coeliac trunk artery, and proper hepatic artery for angiography. Thickening of the branch vessels of the right and left hepatic arteries was observed with tumor staining. The microcatheter was super-selected into the target vessel and the following agents were injected: 5 mg tropisetron, 100 mg oxaliplatin and 1 g fluorouracil.An embolizing agent consisting of 40 mg pirarubicin mixed with iodized oil and polyvinyl alcohol microspheres was used(the dose was adjusted according to the patient's liver function and body surface area). Once the target artery was embolized, and the embolization aggregate was deemed successful, a follow-up angiography was performed again. The

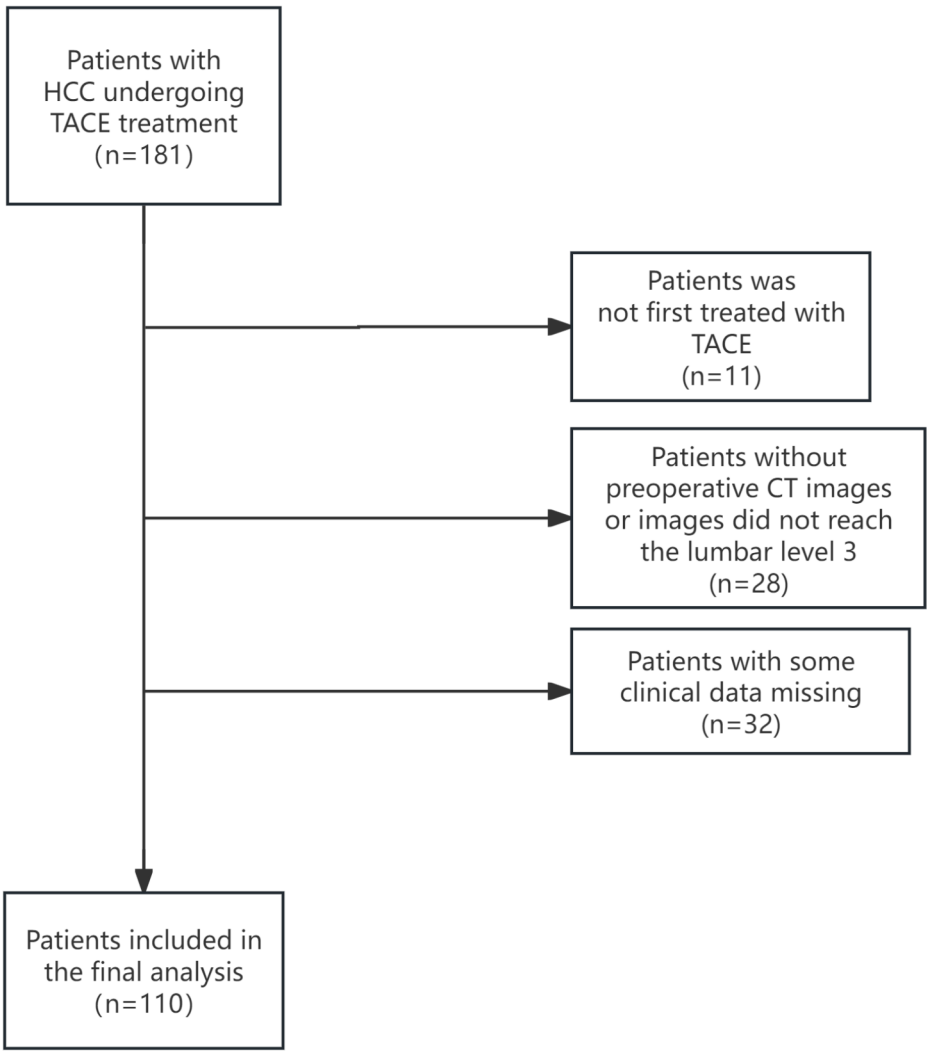

Fig. 1 Flowchart of the inclusion of patients for whose SMI could be evaluated

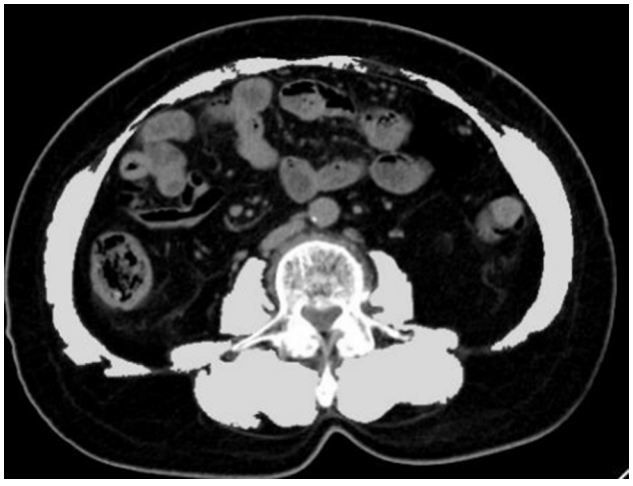

Fig. 2 The white part is the skeletal muscle area

embolization endpoint was achieved when blood flow had stagnated in the supplying artery of the target lesion and tumor staining has disappeared. The catheter series was then withdrawn, local pressure dressing was applied, and the patient was safely returned .

Definition of PES

PES is defined as a syndrome that occurs 1–3 days after TACE in which the patient presents with at least one of the following symptoms: fever>38.5 ℃,gastrointestinal reactions(such as nausea and/or vomiting), and abdominal pain, requiring the use of analgesics.

Statistical analysis

All variables were presented as median[interquartile range(IQR)] for quantitative variables and as count for qualitative variables.Continuous variables conforming to a normal distribution were reported as the

mean±standard deviation ($\bar{x}\pm s$).Patients were classified into two groups according to the presence or absence of PES after TACE and their clinical features were compared. The χ^2test was used to compare categorical variables.while the Fisher's exact test was used for any comparison with fewer than 5 cell counts in a 2×2 contingency table.*T*-test or Mann-Whitney *U*-test was used for continuous variables.Univariable and multivariable logistic regression analyses were performed to determine any associations between low SMI and PES.

Statistical analyses were performed using SPSS version 23.0 for Windows.

Results

Comparison of clinical features with and without PES

A total of 110 patients were included in this study, of whom 82 had PES and 28 did not.In comparing the clinical characteristics of the two groups, serum albumin was found to be significantly lower in the PES group compared to the non-PES group. In addition, there was a significantly higher frequency of HCC with a maximum diameter>3 cm and low SMI in the PES group compared to the non-PES group. The demographic and clinical characteristics of the participants are detailed in Table 1.

Prediction of PES after TACE

Cox univariable analysis was performed for each clinical feature. According to these results, features with $P<0.2$ were included in the Cox multivariable analysis, which revealed that the maximum diameter of HCC>3 cm and low SMI were independent predictors of PES after TACE (shown in Table 2).

Discussion

In this study, HCC with a maximum diameter of >3 cm and low SMI were identified as independent risk factors for PES after TACE treatment.In other words, in addition to tumor load, muscle mass can also affect the short-term prognosis of HCC patients treated with TACE. These findings suggest that changing muscle status before treatment could improve the prognosis of patients.

PES, including transient abdominal pain, nausea, vomiting, and fever, results in prolonged hospitalization and increased postoperative costs during TACE treatment which increases median survival from 16 to 20 months [17]. PES is mainly caused by the embolization of a certain volume of both tumor and normal liver tissue during TACE surgery, resulting in necrosis and edema of the local liver tissue.This leads to a series of symptoms such as liver pain and heat absorption of necrotic tissue.PES not only affects the body's acceptance of TACE surgery, but is also associated with poor overall survival [18].Therefore, it is crucial to identify the influencing factors of PES and preoperative risk stratification.Although there have been many studies on the prediction of postoperative TACE efficacy and overall survival [13, 19–21], fewer studies have addressed PES.In univariate regression analysis, diabetes and serum albumin were protective factors for PES. Previous studies have suggested that diabetes may affect HCC recurrence through hyperinsulinemia, hyperglycemia or chronic inflammation [22], but the relationship between diabetes and PES has not been studied, and need to be further studied and explored.Our study found that patients with high serum albumin are less likely to develop PES than patients with low serum albumin, proved that one of the indexes of Child-Pugh

Table 1 The clinical features of the patients with and without postembolization syndrome included in this study

Variables	Overall *N*=110	Patients with PES *N*=82	Patients without PES *N*=28	t/χ2/Z value	*P* value
Male	87	66	21	0.38	0.538
Age	61.10±9.35	61.89±9.89	58.75±7.18	-1.54	0.126
BMI(kg/m^2)	23.45(20.76,25.66)	23.38(20.54.25.66)	24.27(21.31,25.60)	-1.215	0.225
Hypertension	21	18	3	-	0.268*
Diabetes	12	6	6	4.27	0.039
Platelet(×10^9 /L)	124.5(80.0,190.25)	127.50(85.25,201.75)	120.5(79,178)	-0.494	0.621
Serum albumin(g/L)	36.82±35.57	36.09±6.26	38.93±4.45	2.209	0.029
Total bilirubin(μmol/L)	19.55(15.62,25.80)	19.45(15.27,25.02)	20.20(16.85,28.10)	-0.808	0.385
AFP>400ng/mL	14	11	3	-	1*
Child-Pugh grade(A)	85	62	23	0.50	0.476
HCC Lesion number >3	46	36	10	0.575	0.448
HCC maximum diameter>3 cm	76	64	12	12.105	0.001
Portal vein tumor thrombus	24	20	4	-	0.304*
Metastasis	14	12	2	-	0.512*
L-SMI	91	76	15	22.356	0.000
BCLC stage A/B/C	21/64/25	14/47/21	7/17/4	1.906	0.386

Abbreviations BMI, body mass index; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; L-SMI, low skeletal muscle index; PES, postembolization syndrome.*Fisher's Exact Test

Table 2 Univariable and multivariable cox regression analyses in predicting postembolization syndrome

Characteristics	UV HR (95%CI)	UV *P* value	MV HR (95%CI)2	MV *P* value
Male	1.375(0.498,3.794)	0.539		
Age	1.037(0.990,1.087)	**0.128***	1.053(0.992,1.118)	0.090
BMI(kg/m^2)	0.932(0.834,1.043)	0.220		
Hypertension	2.344(0.634,8.658)	0.201		
Diabetes	0.289(0.085,0.987)	**0.048***	0.313(0.064,1.527)	0.151
Platelet(×10^9 /L)	1.000(0.995,1.006)	0.884		
Serum albumin(g/L)	0.920(0.852,0.993)	**0.033***	0.924(0.837,1.019)	0.114
Total bilirubin(μmol/L)	0.977(0.943,1.012)	**0.194***	0.981(0.935,1.028)	0.414
AFP>400ng/mL	1.291(0.333,5.008)	0.712		
Child-Pugh grade(B)	1.484(0.499,4.416)	0.478		
HCC Lesion number >3	1.409(0.580,3.422)	0.449		
HCC maximum diameter>3 cm	4.741(1.902,11.813)	**0.001***	5.957(1.427,24.86)	**0.014***
Portal vein tumor thrombus	1.935(0.599,6.251)	0.270		
Metastasis	2.229(0.467,10.639)	0.315		
L-SMI	10.978(3.601,33.465)	**0.000***	5.695(1.323,24.513)	**0.020***
BCLC stage(A)				
B	1.382(0.447,4.004)	0.551	0.205(0.039,1.095)	0.064
C	2.625(0.646,10.669)	**0.177***	0.964(0.158,5.866)	0.968

Note *Those variables found significant at $P<0.2$ in univariable analyses were entered into multivariable Cox regression analyses

Abbreviations BMI, body mass index; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; L-SMI, low skeletal muscle index; PES, postembolization syndrome; CI, confidence interval; HR, hazard ratio; MV, multivariable; NS, not significant; UV, univariable

grading can be used as one of the indexes to predict the prognosis of HCC patients after TACE.It has been suggested that the number of tumors may be a predictor of PES after TACE [23], However, while our study found no association the number of tumors and PES, the maximum tumor diameter was identified to be a predictor of PES. This may be due to larger tumors requiring greater doses of chemotherapy drugs. Another study also found age and Child-Pugh not to be sensitive predictors to PES, consistent with the results of this study [24].

More recently, sarcopenia, as a measure of athletic performance and nutritional status, has been established to play an important role in the clinical management and prognosis of HCC patients.However, the relationship between sarcopenia and PES remains unclear.In 2019,a consensus developed by the Asian Working Group for Sarcopenia (AWGS) states that [25] did not include SMI in the diagnostic criteria, but the European Working Group on Sarcopenia in Older Adults identified the CT image of the L3 vertebra as a new tool for assessing muscle mass [26]. The Global Leadership Initiative on Malnutrition (GLIM) consensus also recommends effective methods for measuring body composition, such as CT.There is also strong evidence to support the inclusion of muscle mass loss in the GLIM consensus criteria [27]. Previous studies have indicated that the skeletal muscle mass measured by CT at the waist level is significantly correlated with muscle strength and body status [28]. Therefore, a wide range of studies have adopted the L3 SMI as a measure of sarcopenia.In a multi-center study conducted in China, researchers measured the L3 SMI based on healthy people in physical examination centers to obtain cutoff values: male SMI<44.77 cm^2/m^2 and female SMI<32.50cm^2/m^2 [16], these cutoff values were used in our study to estimate the muscle mass of the patients.

SMI is not only a prognostic factor for HCC patients receiving TACE treatment, but also for those receiving hepatectomy, radiofrequency ablation and other treatments. Low SMI has been associated with the occurrence, recurrence and reduced overall survival of postoperative complications [29–32]. However, there have been no relevant studies on the relationship between SMI and PES. Through retrospective analysis, this study found that low SMI was associated with the occurrence of PES and increases patient pain during treatment. This may be related to the role of the skeletal muscle as an endocrine organ, actively shaping the immune system and regulating innate and adaptive immune responses in a pro- and anti-inflammatory manner.

This study has several limitations. First, as single-center retrospective study, there may be inherent biases and it is a pity that our dates was not so comprehensive for further stratified according to the severity of symptoms.Second, since the diagnosis of HCC relied on imaging, there were insufficient pathological information to discuss the relationship between tumor differentiation and SMI.Furthermore, due to insufficient follow-up in our study no prognostic analysis could be performed.Therefore, the findings should be interpreted with caution and need to be confirmed through prospective studies.

In summary, low SMI is an independent predictor of PES in HCC patients after TACE treatment, suggesting that preoperative CT assessment of skeletal muscle mass can serve as a simple and effective tool for predicting prognosis and help some patiens avoiding the need for overnight inpatient monitoring.

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Author contributions
XW and JW conducted research and wrote articles; XW and LM did image processing; SD、JW and JL did statistical analysis; KL, YZ, RW and QR collected clinic datas; YQ prepared tables. All authors reviewed the manuscript.

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Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and informed consent
The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Xingtai People's Hospital(Approval Letter NO.(2023 [104])). All participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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