Original Article

Nomogram based on intramuscular adipose tissue content for predicting the prognosis of patients with gallbladder cancer after radical resection

Chongming Zheng[1], Xiaotian Chen[2], Zhewei Zhang[2], Anlvna Li[2], Junwei Wang[2], Tingting Cai[2], Yanping Tang[2], Xuewen An[2], Fei Lu[2], Gang Chen[1], Youqun Xiang[3]

[1]Department of Hepatobiliary Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; [2]Wenzhou Medical University, Wenzhou, China; [3]Department of Colorectal Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

Contributions: (I) Conception and design: C Zheng; (II) Administrative support: G Chen, Y Xiang; (III) Provision of study materials or patients: X Chen; (IV) Collection and assembly of data: F Lu; (V) Data analysis and interpretation: Z Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Gang Chen, MD, PhD. Department of Hepatobiliary Surgery, The First Affiliated Hospital of Wenzhou Medical University, Fuxue Road, Wenzhou, Zhejiang 325035, China. Email: chen.gang@wmu.edu.cn; Youqun Xiang, MD. Department of Colorectal Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China. Email: tom502@sina.com.

Background: To investigate the predictive value of intramuscular adipose tissue content (IMAC) on the outcome of gallbladder cancer (GBC) patients after resection, by then develop and evaluate a nomogram to predict the prognosis of GBC patients.

Methods: This research incorporated 123 patients with a pathological diagnosis of GBC. Evaluating the prognosis by the Kaplan-Meier method. Independent predictors of overall survival (OS) were screened using multifactorial Cox regression analysis, and a nomogram was constructed from these. Consistency index and calibration curve were used to identify and calibrate the nomogram. The accuracy of the nomogram was assessed by receiver operating characteristic (ROC) curve and decision curve analysis (DCA) was used to assess the net benefit.

Results: Patients with high IMAC showed a worse prognosis. A nomogram was constructed to predict OS based on IMAC. The C-index for the nomogram was 0.804. The calibration curve showed well performance of the nomogram. The area under the ROC curve (AUC) for the nomogram at three and five years was 0.839 and 0.785, respectively. A high net benefit was demonstrated by DCA.

Conclusions: IMAC was a valid predictor for GBC patients. A nomogram with good performance is constructed to predict the prognosis of GBC patients.

Keywords: Intramuscular adipose tissue content (IMAC); gallbladder cancer (GBC); prognosis; sarcopenia; nomogram

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Introduction

Gallbladder cancer (GBC) is a common malignancy that ranks fifth most common malignant tumor of the gastrointestinal tract (1), it accounts for about 1% of all cancers in China (2). Radical resection is currently the most effective method for the treatment of GBC (3,4), however, less than 10% of patients have access to surgery, and five-year overall survival (OS) rates for GBC patients undergoing radical resection ranged from 21% to 69% (5). Currently, the factor affecting the postoperative outcome of GBC patients is still not unclear, so it is of great importance to find a non-invasive and convenient factor to predict

the postoperative outcome of GBC patients and guide the subsequent treatment strategy.

Sarcopenia is a pathological status characterized by decreased body muscle mass and functional insufficiency due to multiple causes (6,7). Previous studies showed that sarcopenia is a poor prognostic indicator in certain cancers, such as gastric cancer, colorectal cancer, and hepatocellular carcinoma (8-11). Cancer patients with sarcopenia are more likely to experience longer hospital stays, more severe postoperative complications, and poorer prognosis (10). Intramuscular adipose tissue content (IMAC) is a new indicator of sarcopenia, which was associated with skeletal muscle quality, was initially considered to be related to the severity of nonalcoholic steatohepatitis (NASH) (12). It has been reported that IMAC is related to poor outcomes after hepatectomy for hepatocellular (13) and after hepatectomy for colorectal liver metastasis (14). However, the predictive effect of IMAC on GBC is still unclear.

As a visualization of multifactorial models, nomogram is currently one of the most widely used clinical prediction tools. Though previous studies have constructed various nomograms in an attempt to predict the postoperative prognosis of GBC patients (15,16), there is no nomogram based on sarcopenia index to predict postoperative outcomes of GBC patients.

This study aims at evaluating the prognostic value of IMAC to those who suffer from GBC. In addition, constructing and verifying a nomogram based on IMAC to predict the OS of GBC patients. We present the following article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-123/rc).

Methods

Patients

The retrospective study incorporated patients who underwent radical resection and had pathologically confirmed GBC from the First Affiliated Hospital of Wenzhou Medical University. From January 2008 to November 2020, 123 patients were included in this study. The inclusion criteria for patients with GBC were as follows: (I) underwent radical resection and the pathological diagnosis was confirmed as primary GBC; (II) no other preoperative anti-tumor treatment; (III) no other malignant tumor other than GBC; (IV) complete preoperative clinical information was available, including hematological indexes and L3 plane computed tomography (CT) plain images. The exclusion criteria for GBC patients were as follows: (I) pathologically confirmed as non-primary GBC; (II) perioperative death; (III) no complete clinical information including hematological indexes and L3 psoas CT plain scan images for the first diagnosis; (IV) no complete follow-up data.

Image analysis

We used third lumbar (L3) plane CT images within 2 weeks preoperatively to assess whole-body muscle condition. Measurement of skeletal muscle cross-sectional area (cm^2) and CT values (Hounsfield units) in the L3 plane region using ImageJ software. IMAC and psoas muscle mass index (PMI) are calculated according to the method previously reported (14,17). The multifidus muscle was accurately depicted on the L3 level CT image, and its CT value was calculated by ImageJ software (*Figure 1*). The CT value of four subcutaneous fat regions of interest (ROIs) far away from blood vessels was measured, the CT value of subcutaneous fat is expressed as the average CT value of the four ROIs. Muscle mass was assessed by two medical imaging students who are unaware of the patient's clinical and prognostic information. The PMI and IMAC are calculated as follows: PMI = total psoas muscle mass areas (cm^2)/$hight^2$ (m^2). IMAC = CT value of multifidus muscle/CT values of subcutaneous fat.

Clinical and operative characteristics

The clinicopathological characteristics of each patient were collected including: (I) Basic information, including gender, age, body mass index (BMI), diabetes, hypertension, and symptoms. (II) LABORATORY parameters, including carbohydrate antigen 19-9 (CA19-9), serum triglyceride, albumin, lymphocyte absolute value, neutrophil absolute value, high-density lipoprotein (HDL), and total bilirubin. Using laboratory parameters we calculated the prognostic nutritional index (PNI) and the fibrinogen albumin ratio (FAR), which were considered to be associated with the prognosis of numerous tumor patients (17-20). (III) Pathological parameters, including TNM stage (AJCC 8^{th}) and tumor differentiation. All available data in the medical record system is used as much as possible for the construction of predictive models.

Follow-up

The follow-up included survival status, OS is defined as the

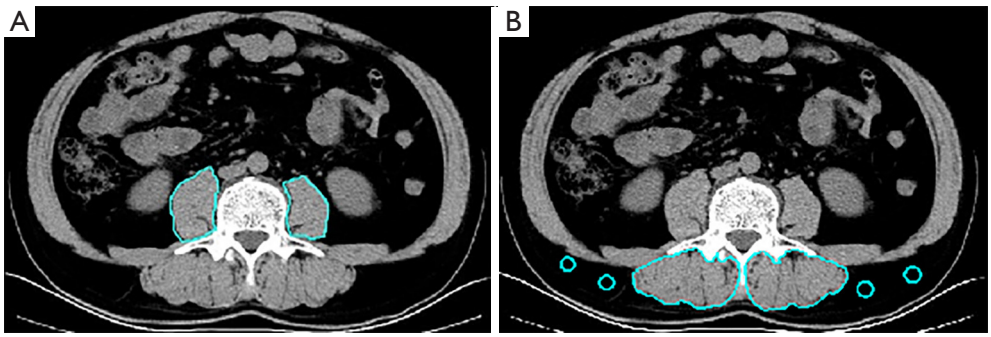

Figure 1 CT images at the L3 plane. (A) Precisely depict bilateral psoas major muscle. The PMI was calculated by normalizing the psoas major muscle to height (cm^2/m^2). (B) CT values of bilateral multifidus muscles and ROIs of four subcutaneous fat were measured. IMAC is the ratio of CT value of bilateral multifidus muscles to the CT value of subcutaneous fat. CT, computed tomography. PMI, psoas muscle mass index; ROI, region of interest; IMAC, intramuscular adipose tissue content.

interval from the first operation to death or the last follow-up. All patients were followed up every three months in the first year and every six months thereafter. The deadline for follow-up was 4th June 2021. The follow-up personnel had no knowledge of the patient's clinical information.

Statistical analysis

Normally distributed continuous variables are demonstrated as mean ± SD, non-normally distributed variables are demonstrated as median and quartile range, and the categorical variables are reported as frequency and percentage. Baseline characteristics were compared between groups using the Pearson chi-square test. Using X-tile software to calculate the cut-off value of IMAC. Using the K-M method to analyze and depict the survival curve. Cox proportional hazards regression model was used to identify independent prognostic factors. In univariate analysis, variables with P value less than 0.1 were selected into the multivariate model. Based on the results of multivariate analysis, the nomogram of OS is established. Harrell consistency index (C index), calibration curve, and decision curve analysis (DCA) were used to evaluate the prediction performance of the nomogram. All statistical data were generated using R, version 4.0.5 (R packages "survminer", "stdca", "survival", "ggplot2", "forestplot", "rms", "timeROC"). Significance was indicated by P value <0.05.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Research Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, and informed consent was taken from all individual participants.

Results

Baseline characteristics

A total of 139 patients with GBC were recruited. After exclusion criteria, a total of 123 patients were included in our study cohort. The baseline data of all patients are shown in *Table 1*. The median age of all patients was 67 years, and women accounted for 64.2% of the total number of patients. Most patients (76.4%) had a TNM stage I or II, the mean BMI of all patients was 22.9 kg/m^2 and the median CA19-9 was 16.9 (μ/mL). The median follow-up time was 41.8 months, the three-year survival rate was 0.741, the five-year survival rate was 0.676.

IMAC as a prognosis predictor for GBC patients

We use X-tile software to calculate the cutoff of IMAC as −0.2, and use the cutoff to divide IMAC into two groups of high IMAC group (H group) and low IMAC group (L group), The comparison between H group and L group is shown in *Table 1*. The H group had 37 patients while L group had 86 patients. The incidence of hypertension was significantly higher in H group than in L group (P=0.012), the age of H group was also notably higher than in L group (P<0.001). Otherwise, there were no other differences affecting tumor prognosis between the two groups. The Kaplan- Meier curve is shown in *Figure 2*, which shows that

Table 1 Patient characteristics

Characteristics	Total (n=123)	High IMAC (n=37)	Low IMAC (n=86)	P value
Age (years), median [IQR]	67 [59–73]	72 [67–80]	64 [55–70]	<0.001
Gender, n (%)				
Male	44 (35.8)	12 (32.4)	32 (37.2)	0.612
Female	79 (64.2)	25 (67.6)	54 (62.8)	
Stage (AJCC 8th), n (%)				
I and II	94 (76.4)	30 (81.1)	64 (74.4)	0.637
III and IV	29 (23.6)	7 (18.9)	22 (25.6)	
Differentiation, n (%)				
Well	49 (39.8)	14 (37.8)	35 (40.7)	0.183
Moderate	40 (32.5)	11 (29.7)	29 (33.7)	
Poor	32 (26.0)	10 (27.0)	22 (25.6)	
Undifferentiated	2 (1.6)	2 (5.4)	0	
Gallstone, n (%)				
No	74 (60.2)	20 (54.1)	54 (62.8)	0.364
Yes	49 (39.8)	17 (45.9)	32 (37.2)	
Hypertension, n (%)				
No	80 (65.0)	18 (48.6)	62 (72.1)	0.012
Yes	43 (35.0)	19 (51.4)	24 (27.9)	
Diabetes, n (%)				
No	102 (82.9)	27 (73.0)	75 (87.2)	0.054
Yes	21 (17.1)	10 (27.0)	11 (12.8)	
BMI (kg/m^2), mean (SD)	22.9 (3.13)	23.23 (3.58)	22.78 (2.93)	0.466
CA19-9 (μ/mL), median [IQR]	16.9 [7.5–98.8]	16.6 [4.2–364.1]	17.1 [6.7–108.7]	0.941
PNI, mean (SD)	47.6 (6.2)	46.2 (6.5)	48.1 (7.3)	0.104
Post-op complication ≥ C-D grade 2, n (%)				
Yes	26 (21.1)	7 (18.9)	19 (22.1)	0.693
No	97 (78.9)	30 (81.1)	67 (77.9)	
HDL (mg/dL), mean (SD)	1.09 (0.36)	1.08 (0.38)	1.1 (0.36)	0.791
Total bilirubin (μmol/L), median [IQR]	9 [7–16]	9 [7–12]	9 [7–16]	0.715
Platelet, mean (SD)	235 (7.6)	238.9 (14.6)	233.3 (8.9)	0.737
PMI, n (%)				
≤4.7	37 (30.1)	18 (48.6)	19 (51.4)	0.332
>4.7	86 (69.9)	50 (58.1)	36 (41.9)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total (n=123)	High IMAC (n=37)	Low IMAC (n=86)	P value
Jaundice, n (%)				
Yes	13 (10.6)	5 (38.5)	8 (61.5)	0.706
No	110 (89.4)	32 (29.1)	78 (70.9)	
FAR, n (%)				
>0.0875	75 (61.0)	27 (36.0)	48 (64.0)	0.074
≤0.0875	48 (39.0)	10 (20.8)	38 (79.2)	
Triglyceride, mean (SD)	1.62 (0.95)	1.53 (0.96)	1.65 (0.95)	0.532

PMI, psoas muscle mass index; IMAC, intramuscular adipose tissue content; BMI, body mass index; CA19-9, carbohydrate antigen 199; PNI, prognostic nutritional index; C-D grade, Clavien-Dindo complication classification; HDL, high-density lipoprotein; FAR, fibrinogen-albumin ratio.

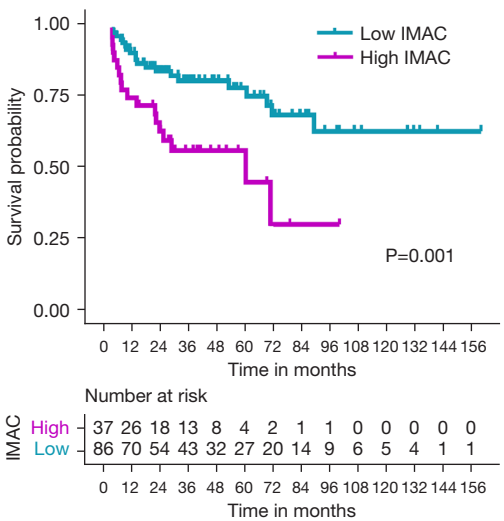

Figure 2 Survival curves for patients with different IMAC. IMAC, intramuscular adipose tissue content.

OS was significantly lower in H group than L group (P<0.05).

Regression analysis

The results of univariate and multivariate factor analysis of the OS in patients with GBC are demonstrated in *Figure 3*. Univariate regression analysis showed that age, TNM stage (AJCC 8th), IMAC, tumor differentiation, CA19-9, HDL, PNI, bilirubin, platelet, triglyceride, FAR, and jaundice as risk factors associated with OS. These twelve risk factors were included in a multifactorial regression model, multifactorial regression showed that TNM stage (AJCC 8th) (HR: 2.886, 95% CI: 1.137–7.327, P=0.026), platelet (HR: 2.771, 95% CI: 1.231–6.241, P=0.014), IMAC (HR: 2.799, 95% CI: 1.169–6.701, P=0.021) and jaundice (HR: 2.628, 95% CI: 1–6.917, P=0.05) were independent risk factors for survival of GBC patients.

Construction and validation of the nomogram

Independent risk factors, including IMAC, TNM stage (AJCC 8th), platelet, and jaundice were selected to plot the nomogram (*Figure 4A*). The C-index of the nomogram was 0.804 (95% CI: 0.949 to 0.659). Calibration curves were plotted (*Figure 4B*), which demonstrate a high agreement between the predicted and actual results of the nomogram. In addition, we evaluated the accuracy of prediction of the nomogram and single parameters (IMAC, TNM stage (AJCC 8th), Platelet, and jaundice using receiver operating characteristic (ROC) curves (*Figure 5A,5B*). The area under the ROC curves (AUC) for nomogram was markedly larger than that of single predictors, with a 3-year predicted survival AUC of 0.839 (0.739–0.939) and a 5-year predicted survival AUC of 0.785 (0.652–0.917). Lastly, the nomogram was compared with single parameters using DCA (*Figure 5C,5D*), the results show that the nomogram has a better net benefit than the individual indicators. Based on these analyses, the nomogram had the best clinical application compared to jaundice, IMAC, TNM staging, and platelets. Therefore, the nomogram is the most suitable model to predict the prognosis in GBC patients and may be useful for clinicians to make therapy decisions and predict prognosis.

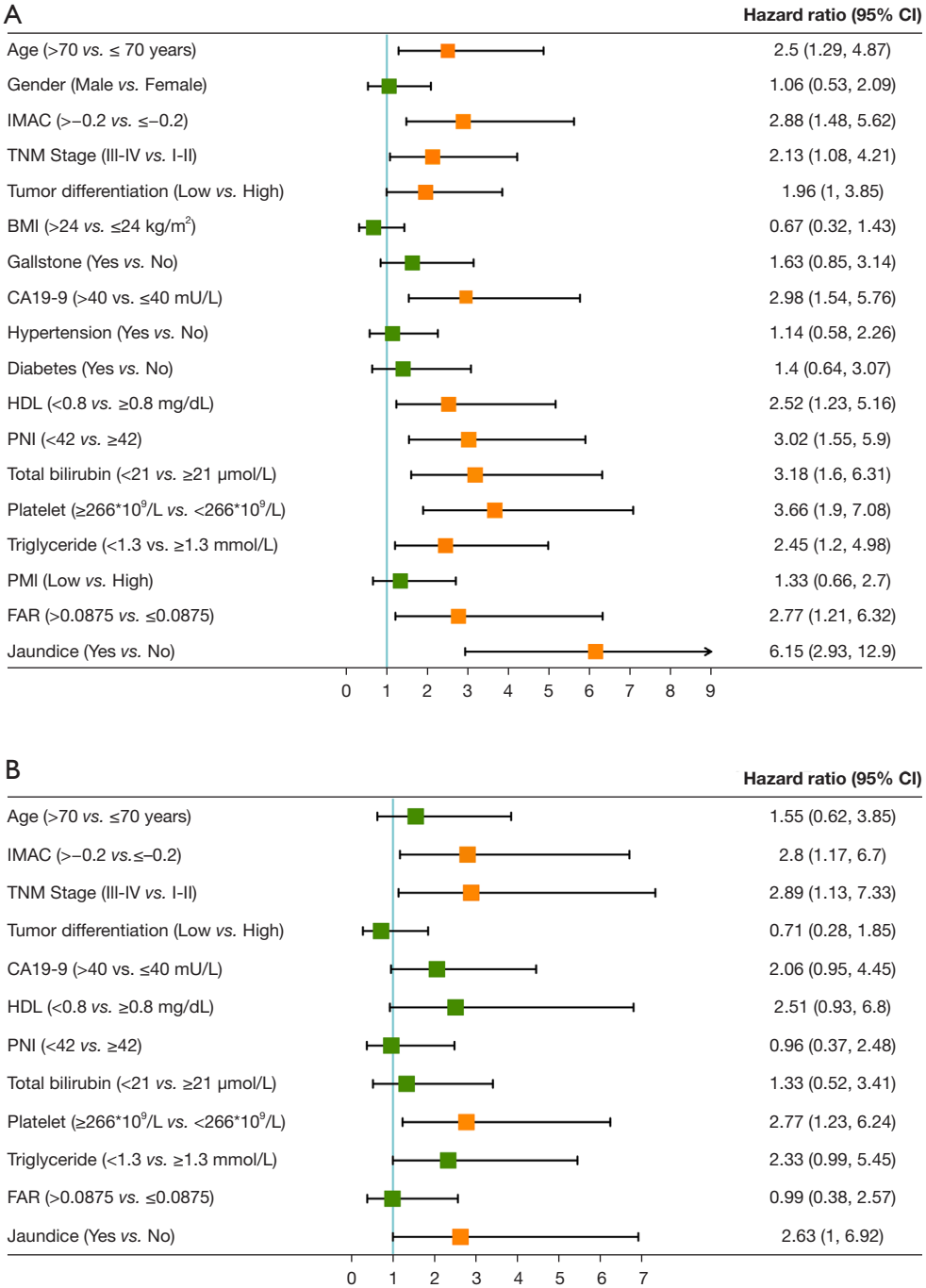

Figure 3 Univariate (A) and multivariate (B) regression analysis of overall survival. IMAC, intramuscular adipose tissue content; BMI, body mass index; CA19-9, carbohydrate antigen 199; HDL, high-density lipoprotein; PNI, prognostic nutritional index; PMI, psoas muscle mass index; FAR, fibrinogen-albumin ratio.

Discussion

An increasing number of studies have shown that skeletal muscle loss (sarcopenia) is an indicator of poor prognosis in cancer patients (17,20-22). However, in previous studies, researchers often focused on the skeletal muscle mass (17,20-22), such as CT plane measurement of skeletal

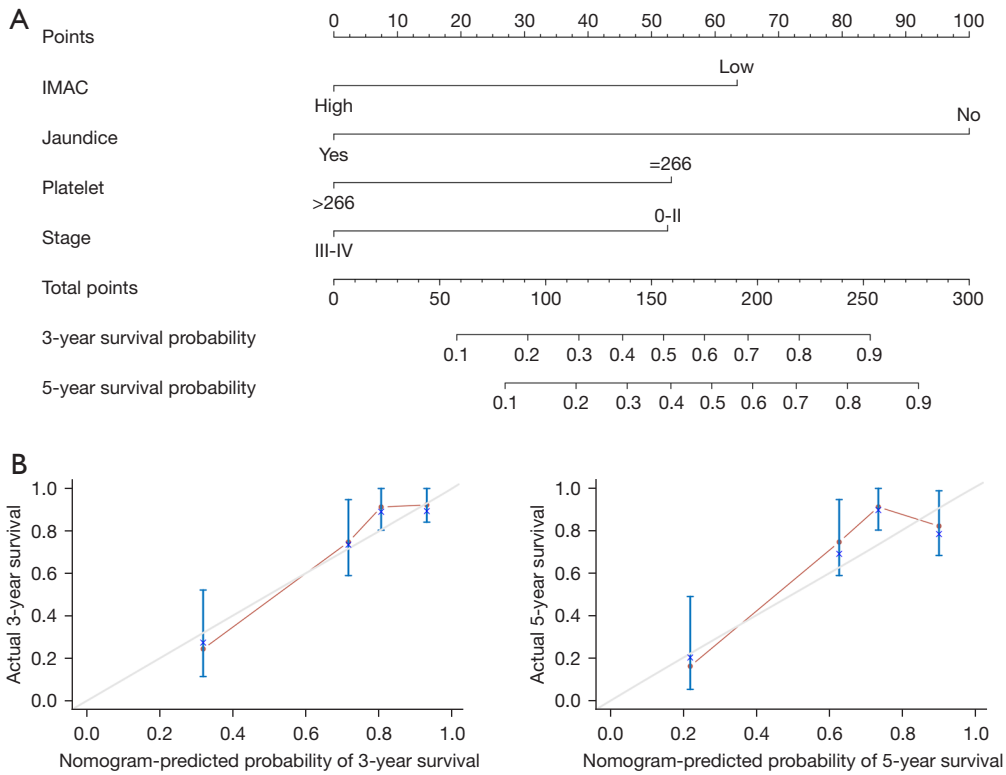

Figure 4 Nomogram and calibration curves. (A) Nomogram based on IMAC, TNM stage (AJCC 8th), platelet, and jaundice for predicting overall survival. (B) Calibration curves for predicting the OS at 3- and 5-year. IMAC, intramuscular adipose tissue content.

muscle area. On the contrary, far less attention has been paid to the degradation of muscle quality caused by muscle fat deposition. Studies have reported the effectiveness of IMAC in predicting the survival of HCC patients (13,23), but the effectiveness of IMAC in predicting the survival of GBC patients has not been reported. In this study, we measured PMI and IMAC of GBC patients and explored the relationship between PMI and IMAC and postoperative survival time of GBC patients. As far as we know, our study found a significant relationship between IMAC and the prognosis of GBC patients for the first time and constructed a nomogram model combined with other indicators.

We found that as an index of skeletal muscle mass, PMI has no significance for the survival of patients with GBC. However, as an index of skeletal muscle quality, IMAC shows excellent predictive ability. This suggests that IMAC may be a better index for the evaluation of sarcopenia than PMI. The reason may be that PMI is expressed by measuring the area of psoas major muscle in the L3 plane, which means that fat will also be included in the measurement. Therefore, skeletal muscle area may not accurately reflect real skeletal muscle condition. IMAC is derived by calculating the CT values of muscle and subcutaneous fat, which can better reflect the muscle loss state of patients. In addition, studies have demonstrated that fat deposition within the skeletal muscle is related to an increased risk of muscle weakness, hypofunction, and activity limitation, as it changes the orientation of muscle fibers and the power generation ability of the whole muscle (24-26). Based on these findings, we believe that IMAC can replace muscle strength and muscle area assessment as the ideal parameter for evaluating sarcopenia.

In our study, the cutoff value of IMAC was calculated by X-tile software and was –0.2 for both men and women, which was different from the previous reports in Japan (male –0.324, female –0.138). These differences may be due to different measurement software and medical imaging equipment and the differences in the population sample.

Although many reports are suggesting that sarcopenia is a factor in the poor prognosis of many tumor patients (17,20-22), the mechanism involved remains unclear. The homeostasis of skeletal muscle is sustained by protein

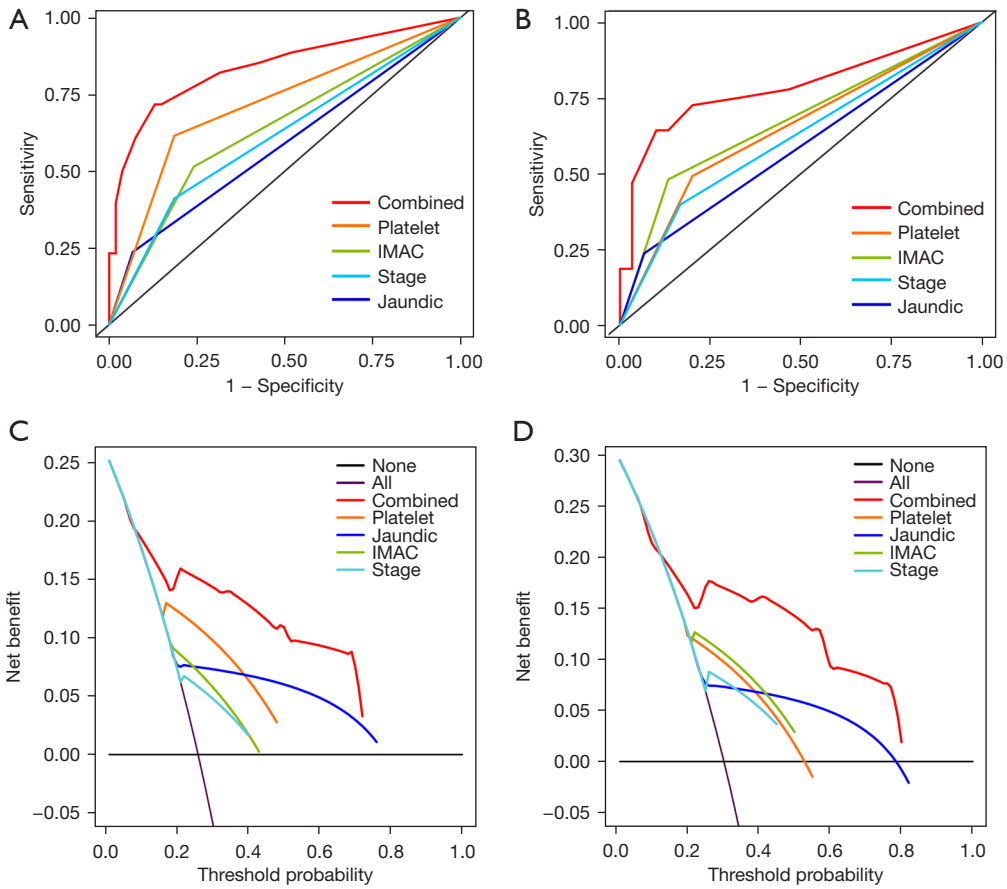

Figure 5 ROC curve and DCA curve of the nomogram for 3- and 5-year survival. (A) The ROC curve of the nomogram at 3-year. (B) The ROC curve of the nomogram at 5-year. (C) The DCA curve of the nomogram at 3-year. (D) The DCA curve of the nomogram at 5-year. IMAC, intramuscular adipose tissue content; ROC, receiver operating characteristic; DCA, decision curve analysis.

synthesis and lecture (27). Nevertheless, for patients with sarcopenia, muscle catabolism is increased (28,29) and the balance of skeletal muscle is disrupted. One reason may be chronic inflammation caused by the presence of cancer cells (30). It has also been shown that with the decrease in skeletal muscle and the increase in adipose tissue, the synthesis, and excretion of various pro-inflammatory adipokines, including leptin and tumor necrosis factor-α, IL-1, and IL-6 are increased. Recently, with the increasing interest in obesity-related tumor subgroups, the interaction between fat and muscle tissue in the occurrence and development of cancer has attracted extensive attention (31). It has been shown that among various adipokines, pro-inflammatory adipokines such as leptin can promote tumor cell growth by activating various growth signaling pathways (32). In addition, anti-inflammatory adipokines such as lipocalin can exert anti-tumor effects through various pathways. Based on these findings, we speculate that increased obesity in sarcopenia patients may lead to an imbalance between adipokines and muscle agonists, leading to cancer growth and recurrence.

The fibrinogen-albumin ratio (FAR) has received wide attention for its effectiveness in predicting the prognosis of patients with numerous malignancies (20,33). Not coincidentally, FAR has been reported as an effective prognostic factor in GBC patients (34). However, our study showed that the P value of FAR was 0.978 (>0.05) in multivariate analysis, which was inconsistent with previous reports, suggesting that FAR may not be an excellent indicator for evaluating the prognosis of patients with GBC. Similarly, as a nutritional index, PNI did not show good validity in multivariate regression analysis (P=0.931). These differences may be due to the insufficient number of patients in our study cohort. In addition, the inclusion of

patients with unexpected GBC caused bias, which may also account for the lack of statistical significance of PNI and FAR on prognosis in our study cohort.

Since the first nomogram for prognosis of GBC was constructed by Wang *et al.* (15), a large number of nomograms of GBC have been constructed based on different indicators. Xiao *et al.* obtained a nomogram based on the log odds of positive lymph nodes (LODDS) by mining the SEER database, the predicted C-index of the nomogram was 0.752 (16). Sun *et al.* built a nomogram based on the immune prognostic index (IPI) for GBC patients, the C-index of this model was 0.791 (35). However, the nomogram for GBC patients based on sarcopenia indicators has not been established. Our current study establishes a nomogram based on sarcopenia indicators of GBC for the first time, the C-index of the nomogram was 0.804, demonstrating the good performance of the model.

Our current study still has several limitations. Firstly, the number of patients we included was insufficient, and our study cohort was from a single center with a small clinical database (the First Affiliated Hospital of Wenzhou Medical University). Due to selection bias and lack of external or internal validation, the results of this study may not be valid for patients at other institutions or regions. Secondly, the follow-up period was too short, 44 patients in our study cohort had the procedure within 3 years. Thirdly, due to the limitation of retrospective study, we can't get the preoperative grip strength and walking speed of patients, which limits us to fully classify the population of sarcopenia.

Conclusions

IMAC is an independent predictor of postoperative prognosis in GBC patients, and high IMAC predicts a poor prognosis. The nomogram based on IMAC could help to make treatment decisions and improve the prognosis of GBC patients.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-123/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-123/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-123/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Research Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, and informed consent was taken from all individual participants.

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