Risk Factors for Postoperative Sarcopenia after Major Hepatectomy for Hepatocellular Carcinoma and Its Association with Postoperative Complications: A Postprint

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Abstract

Background Major hepatectomy for liver cancer carries high surgical risk, and perioperative nutritional status is extremely important for postoperative recovery; however, there are currently few studies investigating postoperative skeletal muscle mass loss (PLSMM) as a predictor of postoperative complications and prognosis. Objective To clarify changes in skeletal muscle index (SMI) in patients after major hepatectomy for liver cancer, and to explore the risk factors for PLSMM and its correlation with postoperative complications. Methods A total of 97 patients who underwent major hepatectomy for liver cancer in the Department of Hepatobiliary Surgery, The Second Affiliated Hospital of Soochow University from July 2018 to August 2022 were selected. Skeletal muscle area at the level of the third lumbar vertebra was measured preoperatively and on postoperative day 5 using CT imaging. The postoperative SMI change rate was calculated, with PLSMM defined as the lowest tertile of SMI change rate, based on which patients were divided into PLSMM and NonPLSMM groups. Baseline data, surgery-related indicators, and postoperative indicators were collected and comparatively analyzed between the two groups. Results Postoperative SMI decrease was observed in 54 patients; there were 32 patients in the PLSMM group (SMI $\leq$ -3.59%) and 65 patients in the Non-PLSMM group (SMI $>$ -3.59%). The PLSMM group had longer operative time, greater blood loss, and higher incidence of microvascular invasion (MVI) than the Non-PLSMM group ($P < 0.05$). The PLSMM group also had longer postoperative hospital stay, higher white blood cell count (WBC) and international normalized ratio (INR) on postoperative day 5, lower fibrinogen (FIB) level on postoperative day 5, and higher overall complication rate than the Non-PLSMM group ($P < 0.05$). Multivariate logistic regression analysis revealed that MVI [OR = 2.751, 95% CI (1.173, 6.642)] and operative time > 210 min [OR = 1.973, 95% CI (1.286, 4.936)] were risk factors for PLSMM in patients after major hepatectomy for liver cancer ($P < 0.05$); furthermore, PLSMM [OR = 2.591, 95% CI (1.173, 6.977)], preoperative sarcopenia [OR = 1.798, 95% CI (1.133, 3.792)], operative time > 210 min [OR = 2.958, 95% CI (0.918, 9.529)], and blood loss > 500 ml [OR = 1.003, 95% CI (1.001, 1.007)] were risk factors for complications in patients after major hepatectomy for liver cancer ($P < 0.05$). Conclusion MVI and operative time > 210 min are risk factors for PLSMM after major hepatectomy, while PLSMM is an independent predictor of postoperative complications and exerts a negative impact on prognosis.

Full Text

Risk Factors for Loss of Skeletal Muscle Mass and Its Correlation with Complications after Major Hepatectomy for Liver Cancer

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Abstract

Background: Major hepatectomy for liver malignancies carries substantial risks. Perioperative nutritional support plays a vital role in postoperative recovery. However, few studies have focused on predicting postoperative complications and prognosis using postoperative loss of skeletal muscle mass (PLSMM) in the acute phase after major hepatectomy.

Objective: To identify changes in skeletal muscle index (SMI) and investigate risk factors for PLSMM, as well as its correlation with postoperative complications after major hepatectomy for liver cancer.

Methods: A total of 97 patients who underwent major hepatectomy for liver cancer in the Department of Hepatobiliary Surgery at the Second Affiliated Hospital of Soochow University between July 2018 and August 2022 were included. Preoperative and postoperative day 5 skeletal muscle area at the third lumbar vertebra level were measured using computed tomographic images. The postoperative change rate of SMI was calculated. PLSMM was defined as the lowest tertile of the percent change in SMI, according to which patients were divided into PLSMM and non-PLSMM groups. Baseline data, surgical indices, and postoperative indicators were collected and analyzed.

Results: SMI decreased in 54 patients postoperatively. Thirty-two and 65 patients were assigned to the PLSMM group (SMI ≤ -3.59%) and non-PLSMM group (SMI > -3.59%), respectively. Compared with the non-PLSMM group, the PLSMM group had longer operation time, greater intraoperative blood loss, and higher rate of microvascular invasion (MVI) ($P < 0.05$). Moreover, the PLSMM group had longer postoperative hospital stay, higher levels of white blood cell count and international normalized ratio, and lower level of fibrinogen on postoperative day 5 ($P < 0.05$). The PLSMM group also showed a higher incidence of overall complications ($P < 0.05$). Multivariate logistic regression analysis indicated that MVI [OR = 2.751, 95%CI (1.173, 6.642)] and operation time >210 min [OR = 1.973, 95%CI (1.286, 4.936)] were risk factors associated with PLSMM ($P < 0.05$). PLSMM [OR = 2.591, 95%CI (1.173, 6.977)], preoperative sarcopenia [OR = 1.798, 95%CI (1.133, 3.792)], operation time >210 min [OR = 2.958, 95%CI (0.918, 9.529)], and blood loss >500 ml [OR = 1.003, 95%CI (1.001, 1.007)] were risk factors associated with postoperative complications ($P < 0.05$).

Conclusion: MVI and operation time >210 min were risk factors associated with PLSMM. PLSMM was an independent predictor of postoperative complications, which negatively affected postoperative outcomes after major hepatectomy.

Keywords: postoperative loss of skeletal muscle mass; sarcopenia; liver neoplasms; major hepatectomy; complications

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Introduction

Primary liver malignancies, including hepatocellular carcinoma and cholangiocarcinoma, are common malignant tumors of the digestive system [1-2]. Clinical outcomes are associated with patient general condition, treatment modality, tumor location, and stage. Currently, hepatectomy remains an important curative treatment for liver cancer [3-4], especially as major hepatectomy offers survival hope for patients with advanced disease or after conversion therapy. However, as a complex procedure, major hepatectomy is highly invasive, with long operation time, substantial blood loss, and high risk. Most patients have preoperative liver dysfunction and are prone to severe postoperative complications [5-7].

Sarcopenia refers to progressive, systemic loss of skeletal muscle mass, strength, and function, representing an important manifestation of malnutrition observed in various cancer surgery patients [8]. Previous studies reported sarcopenia prevalence of 20%-70% [9], particularly common in patients undergoing hepatectomy for liver cancer [10]. Most previous research focused on the impact of preoperative sarcopenia on tumor recurrence and long-term prognosis [11-12]. However, considering that intraoperative blood loss, postoperative infection, and liver dysfunction can directly affect postoperative skeletal muscle mass, changes in postoperative skeletal muscle index (SMI) may better reflect complication occurrence and postoperative recovery status. Currently, few studies have reported acute-phase SMI changes after hepatectomy for liver cancer, and whether postoperative SMI changes affect complications remains unclear. Therefore, this study aimed to clarify SMI changes after major hepatectomy for liver malignancies and investigate the impact of postoperative loss of skeletal muscle mass (PLSMM) on postoperative complications.

Methods

1.1 Study Subjects We selected patients who underwent major hepatectomy for liver cancer in the Department of Hepatobiliary Surgery at the Second Affiliated Hospital of Soochow University between July 2018 and August 2022. Inclusion criteria were: (1) major hepatectomy limited to resection of three or more Couinaud liver segments; (2) postoperative pathology confirming primary liver malignancy. Exclusion criteria were: (1) surgeries involving combined gastrointestinal or pancreatic reconstruction; (2) non-malignant liver diseases such as hemangioma or intrahepatic bile duct stones. A total of 102 patients were initially included, of whom 5 were excluded: 4 due to missing preoperative CT data and 1 due to death within 24 hours postoperatively. Ultimately, 97 patients were included. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University (Approval No.: JD-HG-2022-0017), and all subjects provided informed consent.

1.2 SMI Measurement and PLSMM Definition Preoperative CT examination was performed 1-5 days before surgery to evaluate tumor location, size, and number, and to calculate future liver remnant volume. Routine chest-abdomen-pelvis CT was performed on postoperative day 5 to assess recovery status, including organ/space surgical site infection (SSI), bile leakage, and bleeding. Preoperative and postoperative CT images (image threshold range: -29 HU to +150 HU) were analyzed using imaging software (Neusoft PACS/RIS version 5.5) to measure skeletal muscle area at the third lumbar vertebra (L3) level. Preoperative and postoperative SMI values were calculated as: SMI = L3-level skeletal muscle area (cm^2) / height^2 (m^2). SMI change rate = (postoperative SMI - preoperative SMI) / preoperative SMI $\times$ 100%. PLSMM was defined as the lowest tertile of SMI change rate. Patient skeletal muscle changes are shown in Figure 1 [Figure 1: see original paper].

1.3 Data Collection We collected patient demographics and preoperative baseline indicators: gender, age, weight, BMI, pathological diagnosis, sarcopenia, viral hepatitis, Child-Pugh grade, liver cirrhosis, indocyanine green 15-minute retention rate (ICG-R15), future liver remnant volume, and routine laboratory test indicators. Surgical indicators included: surgical approach, operation time, blood loss, transfusion, microvascular invasion (MVI), etc. Postoperative outcome indicators included: postoperative hospital stay, laboratory tests on postoperative day 5, organ/space SSI, incisional SSI, bacteremia, bile leakage, postoperative bleeding, liver failure, delayed gastric emptying, cardiopulmonary events, thrombotic events, single-organ failure, and mortality.

1.4 Statistical Methods Statistical analysis was performed using SPSS 25.0 software. Non-normally distributed continuous data were expressed as M(P25, P75) and compared between groups using Mann-Whitney U test. Categorical data were analyzed using ^{2} test. Univariate and multivariate logistic regression analyses were used to explore risk factors for PLSMM and postoperative complications after major hepatectomy for liver cancer. $P \leq 0.05$ was considered statistically significant.

Results

2.1 General Characteristics Among the 97 patients, 48 were male and 49 were female. Age ranged from 52-69 years with a median of 60 years. BMI ranged from 20.8-24.8 kg/m^2 with a median of 22.2 kg/m^2. Pathological diagnosis: hepatocellular carcinoma in 59 cases (60.8%) and cholangiocarcinoma in 38 cases (39.2%). Postoperative SMI change rate ranged from -4.826% to 2.124% with a median of -0.194%. SMI decreased in 54 patients postoperatively. According to the predefined criteria (PLSMM defined as the lowest tertile of SMI change percentage), SMI change rate $\leq$ -3.59% was defined as PLSMM, which included 32 patients (Figure 2 [Figure 2: see original paper]).

2.2 Preoperative Baseline Indicators There were no statistically significant differences between the PLSMM and non-PLSMM groups in gender, age, weight, BMI, pathological diagnosis, preoperative sarcopenia, viral hepatitis, Child-Pugh grade, liver cirrhosis, ICG-R15, future liver remnant volume, white blood cell count, hemoglobin, platelet count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, total bilirubin, direct bilirubin, albumin, globulin, albumin-to-globulin ratio, international normalized ratio, prothrombin time, activated partial thromboplastin time, or fibrinogen ($P >$ 0.05, Table 1).

2.3 Surgical Indicators There were no statistically significant differences between the PLSMM and non-PLSMM groups in surgical approach or transfusion rate ($P > 0.05$). However, the PLSMM group had significantly longer operation time, greater blood loss, and higher MVI incidence compared with the non-PLSMM group ($P < 0.05$, Table 2).

2.4 Postoperative Indicators and Complications There were no statistically significant differences between the PLSMM and non-PLSMM groups in hemoglobin, platelet count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, total bilirubin, direct bilirubin, albumin, globulin, albumin-to-globulin ratio, prothrombin time, activated partial thromboplastin time, postoperative bleeding, delayed gastric emptying, or cardiopulmonary events on postoperative day 5 ($P > 0.05$). The PLSMM group had significantly longer postoperative hospital stay, higher white blood cell count and international normalized ratio, lower fibrinogen level, and higher overall complication rate compared with the non-PLSMM group ($P < 0.05$, Table 3).

2.5 Univariate and Multivariate Logistic Regression Analysis of Risk Factors for PLSMM Using PLSMM occurrence as the dependent variable (assignment: no = 0, yes = 1) and gender, BMI, preoperative sarcopenia, viral hepatitis, liver cirrhosis, ICG-R15, future liver remnant volume, operation time, blood loss, transfusion, MVI, and postoperative laboratory indicators as independent variables, univariate logistic regression analysis showed that MVI, operation time >210 min, blood loss >500 ml, white blood cell count >9$×10^{9}$/L, and international normalized ratio >1.3 were risk factors for PLSMM ($P < 0.05$). Multivariate logistic regression analysis revealed that MVI and operation time >210 min were independent risk factors for PLSMM ($P < 0.05$, Table 4).

2.6 Univariate and Multivariate Logistic Regression Analysis of Risk Factors for Postoperative Complications Using postoperative complication occurrence as the dependent variable (assignment: no = 0, yes = 1) and gender, BMI, PLSMM, preoperative sarcopenia, viral hepatitis, liver cirrhosis, ICG-R15, future liver remnant volume, operation time, blood loss, transfusion, MVI, and postoperative laboratory indicators as independent variables, univariate logistic regression analysis showed that PLSMM, preoperative sarcopenia, operation time >210 min, blood loss >500 ml, transfusion, white blood cell count >9$\times10^{\{9\}/L, neutrophilcount > 6\times10}${9}$/L, and albumin <32 g/L were risk factors for complications ($P < 0.05$). Multivariate logistic regression analysis showed that PLSMM, preoperative sarcopenia, operation time >210 min, and blood loss >500 ml were independent risk factors for postoperative complications ($P < 0.05$, Table 5).

Discussion

This study found that although preoperative sarcopenia rates were similar between the PLSMM and non-PLSMM groups without statistical difference, significant postoperative skeletal muscle loss markedly affected patient recovery and complication rates. Specifically, patients with postoperative SMI change rate $\leq$ -3.59% experienced more complicated recovery courses and poorer prognosis. Further risk factor analysis also identified PLSMM as an independent predictor of overall postoperative complications after hepatectomy. Therefore, assessment of skeletal muscle mass in the acute postoperative phase is crucial.

Skeletal muscle mass can be measured using CT, magnetic resonance imaging, dual-energy X-ray absorptiometry, and bioelectrical impedance analysis. However, in the postoperative setting, magnetic resonance imaging and dual-energy X-ray absorptiometry are difficult to perform routinely, and bioelectrical impedance analysis data may have significant errors due to ascites and drainage tubes [13]. This study utilized CT examination, which is not only easily implemented but also provides comprehensive assessment of tumor status and postoperative recovery while clearly displaying skeletal muscle at the L3 level to reflect whole-body skeletal muscle mass [14-15].

Recent studies have identified skeletal muscle loss as an independent prognostic indicator that negatively impacts outcomes in various cancers including esophageal, colorectal, gastric, and pancreatic cancers [16-19]. However, most research has focused on preoperative or long-term postoperative sarcopenia, while acute-phase postoperative skeletal muscle loss and its impact on complications remain unclear. This study clarified SMI changes after major hepatectomy in liver cancer patients, revealing that 56% of patients experienced postoperative SMI reduction. Decreased postoperative SMI predicts reduced postoperative mobility, increased bed rest, and subsequent complications such as pulmonary infection and deep vein thrombosis. Additionally, skeletal muscle represents the body's largest protein reservoir and an important glucose metabolism organ; when skeletal muscle decreases, malnutrition and immune system impairment readily occur, causing abnormal glucose metabolism, increased infection risk, and poor response to exogenous nutritional support. This study found that the PLSMM group had higher overall complication rates than the non-PLSMM group, particularly inflammatory complications such as organ/space SSI, incisional SSI, bacteremia, and bile leakage. Multivariate analysis indicated that >3.59% SMI reduction on postoperative day 5 was an independent prognostic indicator for complications.

As a hypervascular tumor, liver cancer readily develops MVI, with reported incidence rates of 30%-60% depending on clinical stage and pathological features [20], particularly in aggressive tumors that lead to postoperative recurrence and metastasis, affecting disease-free survival [21-22]. This study's multivariate logistic regression analysis found that MVI was independently associated with PLSMM. MVI causes tumor metastasis and destruction of adjacent normal tissues, leading to skeletal muscle loss, which represents an important mechanism for sarcopenia development in liver cancer patients. This study also found that postoperative SMI reduction rate was significantly correlated with operation time and intraoperative blood loss, suggesting that surgical trauma and hypercatabolic state may be primary causes of PLSMM. Long operation time, extensive trauma, intraoperative mechanical ventilation, blood loss, and wound healing substantially increase amino acid demand [23], particularly in patients with postoperative complications, promoting skeletal muscle protein catabolism.

All liver cancer patients experience inflammatory mediator activation postoperatively [24]. In this study, inflammatory complications (organ/space SSI, incisional SSI, bacteremia, and bile leakage) were significantly associated with

PLSMM. Combined with literature reports, inflammatory response is closely related to postoperative skeletal muscle loss and protein synthesis, reflected in laboratory indicators such as white blood cell count, interleukin (IL)-6, and tumor necrosis factor-α (TNF-α) [25], whose levels also negatively correlate with skeletal muscle strength and function [26]. Although this retrospective study could not obtain IL-6 and TNF-α data, white blood cell count on postoperative day 5 was significantly higher in the PLSMM group than in the non-PLSMM group. Multivariate logistic regression analysis identified organ/space SSI and incisional SSI as independently associated with PLSMM. These results suggest that excessive or persistent inflammatory response and inflammatory complications may cause PLSMM in the acute phase after major hepatectomy. Therefore, to prevent severe postoperative skeletal muscle loss and improve recovery and prognosis, multidisciplinary collaborative management including precise preoperative liver assessment, precise hepatectomy, physical therapy, nutritional rehabilitation programs, and anti-inflammatory treatment is essential.

This study has several limitations. First, as a single-center retrospective study, multicenter, large-sample studies are needed for further validation. Second, due to its retrospective design, this study did not collect data on nutritional management and skeletal muscle function testing. Third, further research is needed to investigate whether improving PLSMM can reduce overall complications and improve prognosis after hepatectomy, which represents a key direction for future studies.

In summary, PLSMM is an independent predictor of overall complications in the acute phase after major hepatectomy for liver cancer. Clinical strategies to adequately improve PLSMM may help enhance recovery and prognosis in patients after hepatectomy.

Author Contributions: GAO Dekang conceptualized the research, collected and organized data, and wrote the initial draft; WEI Shaohua was responsible for conceptualization and design; MA Xiaoming collected and organized data; DU Peng revised the manuscript; XING Chungen proposed the research topic and designed the study; CAO Chun was responsible for quality control and final approval of the manuscript and takes overall responsibility for the article; all authors approved the final manuscript.

Conflict of Interest: The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.