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Research Paper

# Sarcopenia predicts postoperative infection in patients undergoing hepato-biliary-pancreatic surgery

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ABSTRACT

*Background:* Operative mortality and morbidity rates after hepato-biliary-pancreatic (BILI) surgery remain high. This study evaluated clinical characteristics and surgical outcomes of patients who underwent BILI surgery and investigated predictors of outcomes by focusing on sarcopenia.
*Materials and methods:* A prospective observational study was performed for consecutive patients who underwent BILI surgery at our institution between June 2013 and May 2014. Sarcopenia was evaluated using computed tomography. Surgical outcomes and the influence of sarcopenia on outcomes were evaluated. Subsequently, the impact of prognostic factors, including sarcopenia, associated with postoperative infections was assessed using multivariate analyses.
*Results:* Total mortality, major complications, and infectious disease rates for all 157 patients were 0%, 9.6%, and 21.7%, respectively. Thirty-eight patients met the criteria for sarcopenia. The sarcopenic group had a significantly higher incidence of infectious complications compared to the non-sarcopenic group (36.8% vs. 17.2%; $P = 0.015$). During multivariate analyses of prognostic factors, sarcopenia (hazard ratio = 2.44; $P = 0.043$) and diabetes mellitus (hazard ratio = 3.07; $P = 0.01$) were detected as independent predictors of postoperative infections.
*Conclusions:* Sarcopenia is an independent preoperative predictor of infection after BILI surgery. Earlier diagnosis and therapeutic intervention for patients with sarcopenia could be useful in the development of comprehensive approaches for perioperative care.


## 1. Introduction

Hepato-biliary-pancreatic (BILI) surgery involving the liver, bile duct, pancreas, duodenum, and other organs is known as one of the most complicated surgical procedures in the field of gastroenterological surgery. The operative technique, surgical instruments, and perioperative management have evolved considerably over the years; however, the operative mortality and morbidity rates after BILI surgery remain high, even at high-volume centers. Concerning pancreaticoduodenectomy, the postoperative mortality and overall morbidity rates have been reported to be 2.8–3.5% and 40.0%, respectively, in nationwide surveys performed in Japan [1,2]. In addition, postoperative mortality and morbidity rates for hepatectomy have been reported to be 2.6% and 14.5%, respectively, in a nationwide survey performed in Japan [3]. Preoperative assessment of prognostic factors for postoperative complications is therefore required to determine surgical eligibility. However, there are few global, acceptable, and clear standards that can objectively and precisely predict postoperative clinical outcomes after BILI surgery.

A recent study suggested that sarcopenia, which is characterized by skeletal muscle depletion and is an objective predictor of frailty, is independently associated with postoperative infectious diseases and poor prognosis in various types of malignancies [4,5]. We have reported that sarcopenia and American Society of Anesthesiologists (ASA) status were independent preoperative predictors of outcomes of patients with hepatocellular carcinoma undergoing hepatectomy [6]. However, the impact of sarcopenia on short-term outcomes remains controversial. A precise preoperative evaluation

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procedure that forecasts postoperative complications is urgently required for safer BILI surgery.

A few prospective studies have focused on surgical site infections after BILI surgery [7,8]; however, few prospective studies have dealt with global postoperative outcomes after BILI surgery and few have focused on sarcopenia in patients with BILI.

Therefore, this prospective observational study was conducted to investigate the short-term outcomes and preoperative predictors (including sarcopenia) of morbidity for patients who have undergone BILI surgery. Hence, we hypothesized that sarcopenia is significantly associated with postoperative complications, especially infections.

## 2. Materials and methods

### 2.1. Patients

This study was approved by the Ethics Committee of the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and Okayama University Hospital and was conducted in accordance with the tenets of the Declaration of Helsinki. We performed an observational study involving consecutive patients who underwent BILI surgery at the Okayama University Hospital (Okayama, Japan) during the 1-year period from June 2013 to May 2014. Inclusion criteria were age >20 years and major BILI surgery including hepatectomy and pancreatectomy. Patients who underwent cholecystectomy, choledochotomy, or resection of the bile duct were excluded. Written informed consent for this study was obtained from the patients before enrollment. Patients were prospectively observed and followed up until discharge after surgery.

### 2.2. Clinical data

For enrolled patients, the following demographic and clinical data were evaluated as preoperative factors: sex, age, height, weight, body mass index (BMI), body surface area (BSA), ASA physical status, laboratory values (albumin level, total lymphocyte count, and total cholesterol level), controlling nutritional status (CONUT) score [9], comorbidities, and etiology of the disease. The ASA physical status was preoperatively evaluated by anesthesiologists. The CONUT score was calculated using the albumin level, total lymphocyte count, and cholesterol level of each patient [9]. Patients were divided into two groups: the normal group (score $\leq 1$) and the undernutrition group (score $\geq 2$). Data regarding the surgical procedure, operative time, and amount of blood loss were recorded as operative factors. Details of the surgical techniques have been reported previously [10,11].

### 2.3. Image analysis and definition of sarcopenia

Diagnostic computed tomography (CT) images obtained within 3 months prior to surgery were chosen and evaluated using a CT image analysis system (Synapse Vincent; Fujifilm Medical, Tokyo, Japan). The total cross-sectional skeletal muscle area (SMA) and psoas muscle area (PMA) at the level of the third lumbar vertebra were measured by assessing preoperative CT images using Hounsfield unit thresholds of −29 to +150 for skeletal muscle [12]. The details of the measuring method are as described previously [6].

In this study, the SMA ($cm^2$) and the PMA ($cm^2$) were divided by BSA ($m^2$) to obtain the SMA/BSA index (SBI; $cm^2/m^2$) and the PMA/BSA index (PBI; $cm^2/m^2$). The SMA ($cm^2$) was also divided by height ($m^2$) to obtain the skeletal muscle index (SMI; $cm^2/m^2$), which is a common method to define sarcopenia [6]. We examined the relationship between SBI and age, PBI and age, and SBI and PBI. Patients with values less than the gender-specific lowest quartile of SBI were considered to have sarcopenia.

### 2.4. Short-term outcomes

For each patient, the following parameters were prospectively collected after surgery: postoperative mortality, morbidity including infectious diseases, and postoperative length of hospital stay. Postoperative morbidity was assessed using the Clavien-Dindo classification [13] according to the major complications that are defined as Clavien grade $\geq 3$. Regarding infectious diseases, the following were examined: wound infection, intra-abdominal abscess, pneumonia, enteritis, urinary tract infection, mycotic infection, and sepsis. Each patient was examined daily by investigators.

### 2.5. Comparison of the impact of the SBI and SMI on outcomes

To validate the accuracy of the SBI in predicting postoperative infections after BILI surgery, multivariate analyses were performed using the conventional definition of sarcopenia by the SMI [6], including the use of same variables. Patients with values less than the sex-specific lowest quartile of SMI were also considered to have sarcopenia (SMI quartile). We then compared the accuracy of SBI and SMI as predictors of postoperative infections.

### 2.6. Statistical analysis

JMP version 10 software (SAS Institute, Cary, NC) was used for statistical analysis. Data are presented as mean, median, and standard deviation for continuous variables. Categorical data are presented as proportions. Differences between groups were assessed using the Mann-Whitney *U* test for continuous variables and Fisher's exact test or chi-square test for categorical variables. To investigate the impact of prognostic factors associated with postoperative infections, we used the Cox proportional hazard model for univariate and multivariate analyses; hazard ratios (HRs) and 95% confidence intervals were also calculated. A P-value $< 0.05$ was considered significant.

## 3. Results

The 157 patients who underwent BILI surgery were considered eligible for this analysis. The clinicopathological characteristics of these patients (90 men [57.3%] and 67 women [42.7%]; mean age, 65.4 ± 12.5 years) are shown in Table 1. One hundred forty-three (91.1%) patients had an ASA physical status score of 1 or 2. Eighty-six (54.8%) patients had normal CONUT scores. The majority of diseases (80.9%) were malignant tumors.

The mean SBI values were 76.8 ± 7.6 $cm^2/m^2$ for men and 61.2 ± 7.8 $cm^2/m^2$ for women (Fig. 1a). The mean SBI was significantly lower for women than for men ($P < 0.001$). The lowest quartiles of the SBI threshold were 71.6 $cm^2/m^2$ for men and 55.3 $cm^2/m^2$ for women. A linear correlation between SBI and age was found for men ($r^2 = 0.08$; $P = 0.01$) but not for women ($r^2 = 0.04$; $P = 0.09$).

The mean PBI values were 9.5 ± 2.2 $cm^2/m^2$ for men and 6.4 ± 1.4 $cm^2/m^2$ for women. The relationship between PBI and age is shown in Fig. 2. PBI was correlated with age ($r^2 = 0.04$; $P = 0.01$). The relationship between SBI and PBI is shown in Fig. 3. SBI was significantly correlated with PBI ($r^2 = 0.51$; $P < 0.001$).

Regarding operative factors, we performed hepatectomy (87 patients), pancreatectomy (67 patients), and hepatopancreatoduodenectomy (3 patients). The mean operative time was 325 ± 98 min and the mean blood loss was 422 ± 458 ml.