Frailty Predicts Severe Postoperative Complication after Elective Hepatic Resection

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Keywords
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Abstract
Background: Frail patients are likely to suffer from postoperative complication, but this assumption has not been well confirmed. Objectives: This study aims to clarify the importance of frailty in patients undergoing hepatectomy for predicting severe postoperative complications. Method: One hundred and forty-three patients aged > 65 years undergoing hepatectomy between 2011 and 2016 were enrolled in this study. The relevance of frailty versus sarcopenia for postoperative outcome was assessed. We defined clinical frailty (CF) as a CF scale > 4. Sarcopenia was defined by the total muscle area at the level of the third lumbar vertebra measured on computed tomography. Results: There were 16 patients (11%) with CF and 80 patients (56%) with sarcopenia. CF was associated with high age ($p < 0.0001$), severe postoperative complications (Clavien-Dindo classification $\geq 3$) ($p = 0.0059$), and postoperative in-hospital stay ($p = 0.0013$). On the other hand, sarcopenia was not associated with postoperative outcome. Logistic regression analysis revealed that only CF was an independent predictor of severe postoperative complication (risk ratio of 4.2; $p = 0.017$). The occurrence of organ/space surgical site infection was significantly higher in the frailty group than in the non-frailty group. Conclusion: CF, but not sarcopenia, is a robust predictor of severe postoperative complications for patients undergoing hepatectomy.
Introduction

Frailty is multidimensional, heterogeneous, and unstable; thus, it is different from disability or ageing alone [1]. Frailty is commonly measured by summative impairment lists and algorithms derived from clinical judgement [1–4]. Since the number of older patients requiring surgical treatment has been increasing with the development of surgery and anesthesia, the preoperative risk for such treatment in older patients needs to be properly assessed in terms of both the cure of disease and the maintenance of the quality of life. Frailty was introduced to be of great importance in predicting surgical outcomes in older patients [4].

Sarcopenia has been recognized to be involved in vulnerability and has been appreciated for reflecting frailty in patients [5]. Sarcopenia is basically determined by evaluating skeletal muscle in many ways, measuring the total skeletal muscle at the level of the third lumbar vertebra (L3), psoas density, psoas volume, and rectus femoris with computed tomography (CT), ultrasonography, or magnetic resonance imaging [6–9]. The clinical impact of sarcopenia on postoperative morbidity and mortality has been reported so far; but the outcome of such investigations depends on both the surgical procedure and method of measuring sarcopenia [9–14].

Hepatic resection is a widely accepted curative treatment for patients with liver cancer or biliary tract carcinoma. Although the surgical procedure and the management of anesthesia have advanced, hepatectomy is not without problems of morbidity and mortality. Perioperative mortality ranged from 0 to 14.8% around the world in the past two decades and occurs in <2% of the patients in Japan [15, 16]. Recently, postoperative morbidity and mortality for both patients with hepatocellular carcinoma and patients with colorectal liver metastasis turned out to be not only associated with short-term outcomes but also with poorer long-term outcomes [17, 18]. Thus, the effort of decreasing severe postoperative complication is of great importance not only for the economic perspective but also for the prognostic perspective.

We have prospectively evaluated patients’ frailty with clinical frailty scale (CFS) for selecting patients requiring extended perioperative rehabilitation and promoted enhanced recovery of surgery [2]. The aim of the current study is to assess the clinical impact of frailty on postoperative outcome in patients undergoing hepatic resection. Since sarcopenia has already been shown to be involved in predicting the surgical outcome in patients undergoing hepatectomy [19], we here compared the clinical impact of frailty to that of sarcopenia.

Patients and Methods

Patients

This observational study included 143 patients aged >65 years who underwent elective, curative surgery for histologically confirmed colorectal cancer at the Saiseikai Kumamoto Hospital between January 2011 and August 2016. Data collected from inpatient records included demographic data and tumor-specific data. Nutritional status of the patients was also examined by the prognostic nutritional index (PNI) [20] calculated based on the serum albumin concentration and peripheral blood total lymphocyte count. Written informed consent was obtained before surgery. Since the previous report suggested that high-risk surgical procedures such as anterior segmentectomy, central bisegmentectomy, or total caudate lobectomy were associated with the occurrence of bile leakage after hepatectomy [21], we assessed if the surgical procedure was associated with the outcome. This study was approved by the Human Ethics Review Committee of Saiseikai Kumamoto hospital (Kumamoto, Japan).

Assessment of CFS

Frailty was assessed with CFS introduced by Rockwood et al. [2] based on clinical judgement. CFS 1 (Very fit): robust, active, energetic, well-motivated, and fit; these people commonly exercise regularly and
are in the fittest group for their age; CFS 2 (Well): without active disease but less fit than people in category CFS 1; CFS 3 (Well with treated comorbid disease): disease symptoms are well controlled compared with those in category CFS 4; CFS 4 (Apparently vulnerable): although not frankly dependent, these people commonly complain of being “slowed up” or having disease symptoms; CFS 5 (Mildly frail): limited dependence on others for instrumental activities of daily living; CFS 6 (Moderately frail): help is needed with both instrumental and noninstrumental activities of daily living; CFS 7 (Severely frail): completely dependent on others for the activities of daily living or terminally ill. In this study, we determined frailty as CFS ≥4.

**CT Image Analysis and Sarcopenia**

The skeletal muscle area was retrospectively measured on CT scans performed before surgery at the level of the L3 in the inferior direction with the patient in the supine position. Briefly, we used a three-dimensional image analysis system to measure pixels using a window width of −30 to 150 HU to delineate the muscle compartments and compute the cross-sectional area of each in centimeters squared (cm²). The cross-sectional area of muscles (cm²) at the L3 level computed from each image was normalized by the square of the height (m²) to obtain the skeletal muscle index (cm²/m²). All measurements and calculations described above were performed by two trained examiners (H.O. and H.N.), both of whom were blinded to the surgical outcomes at the time of quantification. All evaluations were performed independently. In this study, we applied the sarcopenia definition proposed by Martin et al. [8]. According to this definition, sarcopenia is defined as a skeletal muscle index = ([skeletal muscle area at L3] / [height]²) of <43 cm²/m² in males with a BMI of <25, <53 cm²/m² in males with a BMI of ≥25, and <41 cm²/m² in females.

**Statistics**

We compared the clinical characteristics between the two groups using a χ² analysis for noncontinuous variables and the t test or the Wilcoxon test for continuous variables. We conducted a logistic regression analysis to determine the associations between clinicopathologic factors and severe postoperative complication. Interobserver agreement for image findings of tumor was determined by calculating the κ coefficient. All reported p values are two-sided, and p < 0.05 was considered statistically significant. All analyses were performed using the commercial software (JMP Version 10®; SAS Institute, Cary, NC, USA).

**Results**

**CFS Is Associated with Postoperative Outcomes in Patients Undergoing Hepatectomy**

To objectively evaluate CFS, the interobserver agreement of frailty (CFS ≥4) was measured by the kappa statistic. Kappa was calculated to be 0.769, suggesting that agreement was substantial. There were 16 (11.2%) frail patients. Frailty was associated with high age (p < 0.0001), biliary reconstruction (p = 0.0250), sarcopenia (p = 0.0345), high incidence of severe complication (p = 0.0059), and postoperative length of stay (p = 0.0126) (Table 1). On the other hand, frailty showed no significant correlation with a high BMI and PNI.

**Sarcopenia Is Not Associated with Postoperative Outcomes in Patients Undergoing Hepatectomy**

There were 80 (55.9%) sarcopenic patients. Sarcopenia was associated with female (p = 0.0067) and low BMI (p < 0.0001). However, sarcopenia had no correlation with postoperative outcomes such as severe complication and postoperative length of stay (Table 2).

**CFS Is an Independent Factor Predicting Severe Postoperative Complication in Patients Undergoing Hepatectomy**

There were 30 Clavien 3/4 complications among 143 patients (21.0%). The distribution of Clavien 3/4 complications was as follows: bile leakage (n = 9), organ/space surgical site infection (SSI [n = 13]), intraperitoneal bleeding (n = 1), pleural effusion (n = 2), brain infarction (n = 2), hypercapnia (n = 1), and anastomotic bleeding (n = 1). There was no mortality. Univariate and multivariate analysis of frailty and other perioperative risk factors
are shown in Table 3. Multivariate regression analysis identified only frailty as an independent predictor of the development of severe complications (odds ratio, 4.19; CI 1.30–13.58; \( p = 0.0171 \)). Detailed analysis on severe complications revealed that the incidence of organ/space SSI was significantly higher in the frailty group than that in the non-frailty group among all severe complications (\( p = 0.0049 \)) (Table 4).

**Discussion**

The current study firstly indicates that frailty, but not sarcopenia, has a robust impact on the incidence of severe postoperative complications in patients undergoing hepatectomy. Vulnerability could be easily assessed by general appearance at the first checkup; however,
the quantification of the vulnerability has not been established. We focused on CFS, which is easy to use based on the clinical judgement and powerfully correlates to the surgical outcome. Score ≥ 4 was determined as frailty in the current study. The basic concept of this setting is that patients who somehow slow up, require some support for daily life, or suffer from disease are likely to have life-threatening morbidity after surgical treatment irrespective of medicines they are taking or previous illness such as brain infarction, chronic kidney disease, and heart failure. Correlation of CFS and other established measurement tools such as the frailty index based on clinical deficits has already been confirmed [2], and we also confirmed it in the beginning of the study at our institution. As a result, prospective data collection demonstrated that frailty has a clear and robust correlation with severe complications after curative surgery in patients undergoing hepatectomy.

Although frailty is correlated with sarcopenia, sarcopenia by itself was never correlated with any postoperative outcomes in this study. Recently, sarcopenia was associated with postoperative morbidity and mortality in patients undergoing hepatectomy. Although we assessed the skeletal muscle on CT scans, there are many ways of assessing sarcopenia, and the surgical outcome seems to be dependent on how to quantify sarcopenia. By quantifying the total muscle area at the level of the L3 as we did in the current study, sarcopenia was not

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**Table 3.** Multivariate logistic regression analysis for severe postoperative complication

| Variable                     | Univariate, p value | Multivariate, odds ratio (95% CI) | p value |
|------------------------------|---------------------|----------------------------------|---------|
| Male                         | 0.5661              |                                  |         |
| Age ≥ 74 years               | 0.3591              |                                  |         |
| 2/3 sectionectomy            | 0.0327              | 2.00 (0.69–5.60)                 | 0.1989  |
| High-risk surgical procedures b | 0.7375              | 1.67 (0.46–5.66)                 | 0.4253  |
| Biliary reconstruction       | 0.0293              |                                  |         |
| Experienced operator         | 0.7208              |                                  |         |
| Operation time ≥ 337 min     | 0.0443              | 1.49 (0.56–4.03)                 | 0.4192  |
| Bleeding ≥ 320 g             | 0.0244              | 2.02 (0.80–5.34)                 | 0.1355  |
| Sarcopenia                   | 0.6147              |                                  |         |
| Frailty                      | 0.0057              | 4.19 (1.30–13.58)                | 0.0171  |

*a* Median values are used for the cutoff value. *b* Anterior segmentectomy, central bisegmentectomy, or total caudate lobectomy [21].

**Table 4.** Severe complications (Clavien-Dindo classification 3/4)

| Clinicopathological factors | Frailty (+) (n = 16) | Frailty (−) (n = 127) | p value |
|-----------------------------|-----------------------|-----------------------|---------|
| Total                       | 8 (50)                | 22 (17)               | 0.0059  |
| Bile leakage                | 2 (13)                | 7 (6)                 | 0.5902  |
| SSI (organ/space)           | 5 (31)                | 8 (6)                 | 0.0049  |
| Intrapleural bleeding       | 0                     | 1 (1)                 | 0.5564  |
| Pleural effusion            | 0                     | 2 (2)                 | 0.5326  |
| Brain infarction            | 1 (6)                 | 1 (1)                 | 0.5326  |
| Hypercapnia                 | 0                     | 1 (1)                 | 0.5564  |
| Anastomotic bleeding        | 0                     | 1 (1)                 | 0.5564  |

Figures in parentheses are percentages. SSI, surgical site infection.
associated with the postoperative complication rate in patients with colorectal liver metastasis undergoing hepatectomy [13]. On the other hand, by quantifying psoas area, sarcopenia was associated with Clavien grade ≥3 complication in patients with colorectal liver metastasis undergoing hepatic resection [19]. By quantifying psoas volume, sarcopenia was associated with postoperative Clavien-Dindo ≥3 complication in patients undergoing hepatic resection or liver transplantation [22]. By quantifying psoas density, sarcopenia was associated with 1-year mortality in patients undergoing hepato-pancreato-biliary surgery, whereas psoas area was not efficient for assessing sarcopenia [12]. Since we did not try other methods of assessing sarcopenia, it is possible that sarcopenia might not have been properly determined in our patient cohort.

Given the previous investigations focusing on the impact of nutritional index on postoperative complications [23], we speculated that the nutritional index might partially be the cause or outcome of frailty. If frail patients are also impaired in taking the nutrition, we expected that they could be supported by nutritional intervention before or after surgery. However, there was no significant correlation between PNI and frailty index. Frailty defined by CFS is fundamentally discriminated from nutritional disorder and thereby does not seem to be supported by perioperative nutritional intervention.

Since robust correlation between frailty and morbidity was confirmed in the current observational study, our next concern is if improvement of frailty before surgery could decrease morbidity. In patients undergoing lung resection, preoperative exercise-based training improves pulmonary function before surgery and reduces in-hospital length of stay and postoperative complications [24]. Given the previous exploratory investigations [25, 26], surgical short outcome such as length of stay and the occurrence of complication did not dramatically improve by the intervention of rehabilitation before surgery, suggesting that not all patients (including fit patients) but frail patients might be appropriate candidates for preoperative intervention of those prehabilitation measures to reduce the high possibility of severe postoperative complication.

In conclusion, frailty, but not sarcopenia, independently predicts severe complication in patients undergoing hepatic resection and therefore needs to be clinically emphasized with careful attention. Frailty is conceptually accepted as being similar to sarcopenia, but not eventually collaborative with it based on the current study. The current study suggests that the management of deep/organ SSI should be considered for frail patients undergoing hepatic resection, and further intervention of perioperative rehabilitation should be addressed.

**Statement of Ethics**

All patients enrolled in this study have given their written informed consent. The study protocol has been approved by the institute’s committee on human research.

**Disclosure Statement**

The authors have no conflicts of interest to disclose.

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Author Contributions

Study design: Okabe H., Osaki T., and Takamori H.
Collection of data: Hayashi H., Higashi T., Nitta H., Ikuta Y., Yusa T., Takeyama H., Ogawa K., Ozaki N., Akahoshi S., and Ogata K.
Edition of the manuscript: Baba H.

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