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Original Article

Sarcopenia and American Society of Anesthesiologists Physical Status in the Assessment of Outcomes of Hepatocellular Carcinoma Patients Undergoing Hepatectomy

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Sarcopenia following liver surgery has been reported as a predictor of poor prognosis. Here we investigated predictors of outcomes in patients with hepatocellular carcinoma (HCC) and attempted to establish a new comprehensive preoperative assessment protocol. We retrospectively analyzed the cases of 254 patients who underwent curative hepatectomy for HCC with Child-Pugh classification A at our hospital between January 2007 and December 2013. Sarcopenia was evaluated by computed tomography measurement. The influence of sarcopenia on outcomes was evaluated. We used multivariate analyses to assess the impact of prognostic factors associated with outcomes, including sarcopenia. Of the 254 patients, 118 (46.5%) met the criteria for sarcopenia, and 32 had an American Society of Anesthesiologists (ASA) physical status ≥ 3. The sarcopenic group had a significantly lower 5-year overall survival rate than the non-sarcopenic group (58.2% vs. 82.4%, $p = 0.0002$). In multivariate analyses of prognostic factors, sarcopenia was an independent predictor of poor survival (hazard ratio [HR] = 2.28, $p = 0.002$) and poor ASA status (HR = 3.17, $p = 0.001$). Sarcopenia and poor ASA status are independent preoperative predictors for poor outcomes after hepatectomy. The preoperative identification of sarcopenia and ASA status might enable the development of comprehensive approaches to assess surgical eligibility.

Key words: sarcopenia, American Society of Anesthesiologists physical status, hepatectomy, hepatocellular carcinoma, prognostic factor

Hepatocellular carcinoma (HCC) is the fifth-leading cause of cancer-related deaths in Japan [1] and the third-leading cause of cancer-related deaths worldwide [2]. Hepatectomy is one of the standard treatments for HCC. Advances in surgical techniques and perioperative management have improved the in-hospital mortality rate after surgery and the overall survival rate for HCC; however, further advances in surgical techniques are required to prevent the recurrence of intrahepatic or extrahepatic HCC that often occurs after a hepatectomy [3,4]. A preoperative assessment of prognostic factors is thus required to determine the appropriate treatment, including surgery. To identify the prognostic factors in patients with HCC, previous studies have focused on host-spe-

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cific and tumor-specific factors related to clinical outcomes [5]. However, a comprehensive assessment of the preoperative prognostic factors has not yet been established.

The American Society of Anesthesiologists (ASA) physical status classification system has been used to evaluate the general preoperative condition of patients and was reported to be a predictor of poor outcome following hepatectomy [6,7]. A recent study suggested that sarcopenia, which is characterized by skeletal muscle depletion and is an objective predictor of frailty, is independently associated with poor outcomes in many types of cancers [8]. Regarding HCC, sarcopenia was recently identified as a poor prognostic factor of long-term outcome after hepatectomy, independent of tumor-specific factors [7,9], and is reportedly linked to chemotherapy toxicity [10]. Sarcopenia was also identified as a poor prognostic factor for liver transplantation [11-14]. However, the definition of sarcopenia remains controversial, and a precise preoperative evaluation method that detects sarcopenia, in combination with other predictors, is urgently required for safer hepatic surgery.

We therefore designed the present study to investigate the impact of sarcopenia on overall survival as well as other predictors of overall survival, and to subsequently establish a new comprehensive preoperative scoring system. We hypothesized that sarcopenia is significantly associated with poor prognosis in patients undergoing hepatectomy for HCC.

Materials and Methods

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 (approval no. 1743) and conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, the need for informed consent was waived. We retrospectively reviewed the medical records of consecutive patients who underwent curative resection of HCC at the Okayama University Hospital (Okayama, Japan) in the 7-year period from January 2007 to December 2013. To eliminate the influence of the severity of liver function, the patients enrolled were limited to those with Child-Pugh classification A.

Clinical data. From our database, the following demographic and clinical data were evaluated as preoperative factors: sex, age, height, weight, body mass index (BMI), ASA physical status, etiology of liver disease, laboratory values (albumin level and platelet count), tumor marker levels, liver function evaluated using the Child-Pugh classification, and comorbidities. The ASA physical status was preoperatively evaluated by anesthesiologists.

Surgical procedure and pathological examination. Details of the surgical techniques have been reported [15]. Data for the surgical procedure, type of hepatectomy, operative time, and amount of blood loss were recorded as operative factors. A tumor specimen was evaluated for pathological factors by a pathologist according to the rules of the Liver Cancer Study Group of Japan [16].

Short-term and long-term outcomes. Postoperative complications after surgery were assessed using the Clavien-Dindo classification [17], according to the major complications that are defined as Clavien grade ≥ 3. All patients underwent a follow-up examination every 3 or 6 months at our institution or another affiliated hospital to examine their physical condition, liver function, and recurrence. The last data of this cohort were updated in February 2016.

Image analysis and definition of sarcopenia. Diagnostic computed tomography (CT) images taken within 3 months prior to surgery were chosen and evaluated using a CT image analysis system (Synapse Vincent, Fujifilm Medical, Tokyo). The total cross-sectional skeletal muscle area at the level of the third lumbar vertebra (L3) was measured by assessing preoperative CT images using Hounsfield unit thresholds of -29 to $+150$ for skeletal muscle (Fig. 1) [18]. The L3 region includes the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal oblique abdominal muscles, and the rectus abdominis muscle.

In this study, the skeletal muscle area (cm^2) was divided by height (m^2) to obtain the skeletal muscle index (SMI, cm^2/m^2). The sex-specific cut-off values for the SMI associated with overall mortality obtained by optimum stratification [19,20] were 46.4 cm^2/m^2 for men (area under the curve [AUC] = 0.656) and 37.6 cm^2/m^2 for women (AUC = 0.561). Patients with values below these cut-offs were considered to have sarcopenia.

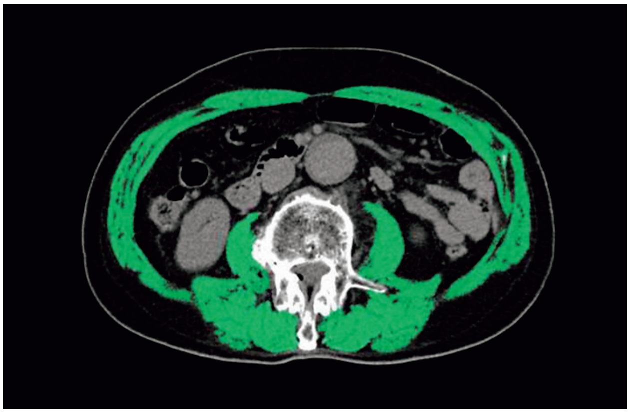

Fig. 1 CT scan of the L3 region showing the total skeletal muscle mass (green).

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 χ^2-test for categorical variables. Overall survival curves were calculated using the Kaplan-Meier method and analyzed using the log rank test. To investigate the impact of prognostic factors associated with overall survival, we used the Cox proportional hazard model for univariate and multivariate analyses, and hazard ratios (HRs) and 95% confidence intervals were calculated. A p-value < 0.05 was considered significant.

Results

Of the 273 patients who underwent curative resection and who were considered eligible for this analysis, 12 were excluded because of unavailable preoperative CT images, and 7 were excluded for a Child-Pugh classification B. The clinicopathological characteristics of the remaining 254 patients (207 men [81.5%], 47 women [18.5%]), with a mean age of 65.7 ± 10.5 years, are shown in Table 1. Thirty-two (12.6%) of the patients had an ASA physical status of 3 or 4. The mean SMI values were 47.6 ± 7.3 cm^2/m^2 for men and 37.4 ± 5.3 cm^2/m^2 for women, and 118 patients (46.5%) were categorized as being sarcopenic.

The sarcopenic group (n = 118) was significantly older ($p < 0.001$) and had significantly lower BMI values ($p < 0.001$) than the non-sarcopenic group (n = 136). The ASA physical status, etiology of liver disease, comorbidities, and operative factors were not significantly different between the 2 groups. With regard to the pathological factors and tumor stage, sarcopenia was correlated with the presence of microvascular invasions ($p = 0.003$) and the tumor stage ($p = 0.015$).

Overall survival after hepatectomy for HCC. Fig. 2 shows the overall survival curves after hepatectomy for HCC for the 2 groups in the Kaplan-Meier analysis. After the median follow-up of 41.8 months (range 1-109 months), 64 patients (25.2%) died from the following causes: cancer progression, 43; liver failure, 5; postoperative mortality, 5; infection, 3; and other reasons, 8. The overall 5-year survival rate was significantly lower in the sarcopenic group compared to the non-sarcopenic group (58.2% vs. 82.4%, log rank $p = 0.0002$).

Prognostic factors for overall survival after hepatectomy for HCC. Table 2 shows the results of the univariate and multivariate analyses to identify the prognostic factors closely related to long-term survival after hepatectomy. In the univariate analysis, 9 variables were independently poor prognostic factors. In the multivariate analysis, 4 variables were significantly poor prognostic factors: sarcopenia ($p = 0.002$), ASA physical status of 3 or 4 ($p = 0.001$), the presence of multiple tumors ($p = 0.014$), and microvascular invasion ($p < 0.001$).

Simple scoring system using preoperative risk factors. A simple scoring system was applied for all patients, with 1 point assigned to each significant preoperative risk factor—sarcopenia and ASA physical status of 3 or 4—using a similar HR as in the multivariate analysis except for pathological factors. We divided the patients into three groups according to these potential risk factors: the Risk 0 group (negative for both sarcopenia and poor ASA status, n = 120), the Risk 1 group (positive for either sarcopenia or poor ASA status, n = 118), and the Risk 2 group (positive for both sarcopenia and poor ASA status, n = 16).

Fig. 3 shows the overall survival curves after hepatectomy for HCC for these 3 groups, based on the Kaplan-Meier analysis. The overall 5-year survival rates after hepatectomy were 85.6% for the Risk 0 group, 62.4% for the Risk 1 group, and 22.8% for the

Table 1 Demographic and clinicopathological factors of the HCC patients with or without sarcopenia who underwent hepatectomy

	All patients (n = 254)	Non-sarcopenic (n = 136)	Sarcopenic (n = 118)	p-value
Demographic variables:				
Men/women	207/47	114/22	93/25	0.31 †
Mean age (yrs)	65.7 ± 10.5	63.1 ± 10.3	68.6 ± 10.0	<0.001 *
BMI (kg/m^2)	23.7 ± 3.5	25.2 ± 3.3	22.0 ± 3.0	<0.001 *
Body composition:				
L3 SMI in men (n = 207, cm^2/m^2)	47.6 ± 7.3	52.8 ± 4.7	41.1 ± 3.9	<0.001 *
L3 SMI in women (n = 47, cm^2/m^2)	37.4 ± 5.3	41.8 ± 3.8	33.5 ± 2.9	<0.001 *
ASA physical status:				
Grades 1-2/3-4	222/32	120/16	102/16	0.67 †
Etiology of liver disease:				
HBV and/or HCV	171	89	82	0.49 †
Others	83	47	36	
Laboratory values:				
Alb (g/dl)	4.0 ± 0.47	4.1 ± 0.48	4.0 ± 0.45	0.11 *
Plt (× 10^4/μl)	18.3 ± 8.2	17.4 ± 7.4	19.5 ± 9.0	0.09 *
Tumor markers:				
AFP (ng/ml)	3,689 ± 21,461	1,438 ± 5,650	6,283 ± 30,766	0.77 *
Comorbidity:				
Diabetes	75	35	40	0.15 †
Hypertension	104	58	46	0.55 †
Operative factors				
Type of hepatectomy:				
≥ lobectomy	97	48	49	0.31 †
≤ segmentectomy	157	88	69	
Operative time (min)	285 ± 111	284 ± 97	287 ± 125	0.35 *
Blood loss (ml)	949 ± 965	910 ± 894	994 ± 1,042	0.61 *
Tumor characteristics				
Tumor size (cm)	4.7 ± 3.5	4.2 ± 2.9	5.3 ± 4.1	0.32 *
Tumor number:				
Solitary/Multiple	175/79	95/41	80/38	0.72 †
Poor differentiation	35	16	19	0.32 †
Microvascular invasion	76	30	46	0.003 †
Tumor stage:				
I/II/III/IV	28/110/83/33	16/63/48/9	12/47/35/24	0.015 †
Major postoperative complications	35	16	19	0.32 †
Postoperative mortality	5	1	4	0.13 †

*Mann-Whitney U test, †Fisher's exact test or χ^2-test. Values are mean ± SD unless otherwise indicated.
BMI, body mass index; SMI, skeletal muscle index; ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; HCV, hepatitis C virus; Alb, albumin; Plt, platelet; AFP, alpha-fetoprotein.

Risk 2 group (log rank $p < 0.0001$) (Table 3). In the Cox proportional hazard model, all differences between the Risk 0 group and other groups were significant. The postoperative mortality rate was significantly highest in the Risk 2 group ($p = 0.007$).

Discussion

This retrospective study demonstrated that sarcopenia and poor ASA status are independent predictors of poor overall survival in patients undergoing hepatectomy for HCC, and we identified the efficiency of a simple scoring system using preoperative risk factors that can detect a high postoperative mortality rate and a low survival rate. The primary finding is similar to that of previous reports, in which sarcopenia was associated with overall survival after hepatectomy for HCC [7,9].

Studies aimed at identifying the prognosis after surgery have conventionally focused on tumor-specific

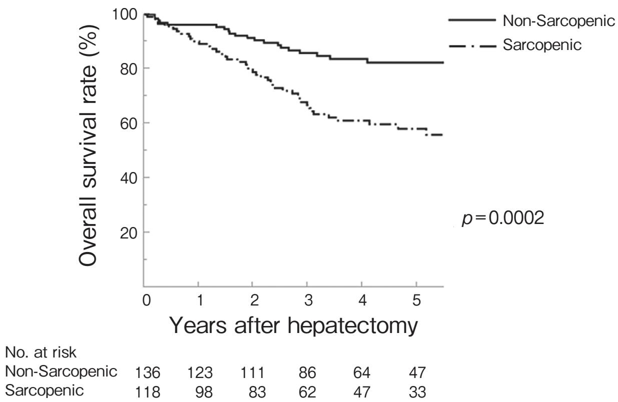

Fig. 2 Overall survival curve after hepatectomy in patients with and without sarcopenia $p = 0.0002$ (log rank test).

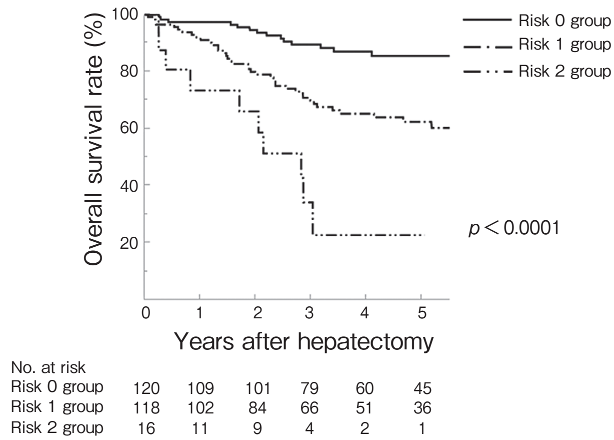

Fig. 3 Overall survival curves after hepatectomy for patients in the Risk 0, Risk 1, and Risk 2 groups. $p < 0.0001$ (log rank test).

Table 2 Univariate and multivariate analyses of prognostic factors associated with overall survival in patients who underwent hepatectomy

	Univariate analysis				Multivariate analysis		
Variable	No. of patients (n = 254)	HR	95% CI	*p*-value*	HR	95% CI	*p*-value*
Sarcopenia	118	2.87	1.72–4.98	<0.001	2.28	1.34–4.01	0.002
Male	207	1.51	0.79–3.28	0.23			
Age (≥70 yrs)	103	1.16	0.70–1.91	0.52			
BMI (≥25 kg/m^2)	83	0.85	0.48–1.44	0.56			
ASA (≥grade 3)	32	3.28	1.80–5.67	<0.001	3.17	1.61–5.94	0.001
HBV and/or HCV	171	0.85	0.52–1.45	0.55			
Alb (<3.6 g/dl)	40	1.43	0.74–2.54	0.27			
Plt (<10×10^4/μl)	33	0.89	0.39–1.76	0.76			
AFP (≥400 ng/ml)	43	1.95	1.07–3.36	0.029	1.00	0.51–1.86	0.99
Diabetes	75	1.96	1.18–3.20	0.01	1.06	0.61–1.82	0.83
Hypertension	104	1.08	0.65–1.77	0.77			
Tumor size (≥50 mm)	77	3.49	2.13–5.73	<0.001	1.23	0.66–2.29	0.52
Tumor number ≥2 tumors)	79	1.91	1.16–3.12	0.012	1.95	1.15–3.31	0.014
Poor differentiation	35	2.58	1.37–4.56	0.005	1.24	0.60–2.40	0.55
Microvascular invasion	76	5.71	3.46–9.62	<0.001	4.04	2.17–7.53	<0.001
Major postoperative complications	35	2.34	1.22-4.17	0.001	1.25	0.60-2.42	0.53

*Cox proportional hazard model.
BMI, body mass index; ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; HCV, hepatitis C virus; Alb, albumin; Plt, platelet; AFP, alpha-fetoprotein.

Table 3 Short-term and long-term outcomes after hepatectomy, based on the results of the risk scoring system

No. of risk factors	Postoperative mortality	*p*-value*	3-year survival rate (%)	5-year survival rate (%)	HR	95% CI	*p*-value†
0 (Risk 0 group, n = 120)	1 (0.83%)	0.007	89.5%	85.6%	–	–	–
1 (Risk 1 group, n = 118)	2 (1.69%)		69.8%	62.4%	3.30	1.84–6.29	<0.0001
2 (Risk 2 group, n = 16)	2 (12.5%)		34.3%	22.8%	9.38	4.00–21.2	<0.0001

*Fisher's exact test or χ^2–test, †Cox proportional hazard model.

factors [5]; however, the prognosis after surgery is multifactorial and depends on not only tumor-specific factors but also preoperative factors of the hosts. Among the preoperative factors, our present findings demonstrated that an ASA physical status ≥ 3 was a significant factor for overall survival, as was sarcopenia. Although the ASA physical status was evaluated by anesthesiologists to assess the surgical risk, it is also useful to assess the general condition of patients.

Gerontologists have focused on frailty to establish a more precise definition of anility [21-23]. Frailty is assessed by a subjective evaluation of unintentional weight loss, exhaustion, weakness, slow walking speed, and low levels of physical activity. Thus, sarcopenia has been investigated as an objective measurement of frailty and a good predictor of poor outcome in various types of cancers [8].

Sarcopenia is defined as a syndrome characterized by the loss of skeletal mass and strength that occurs with aging [24]. The European Working Group on Sarcopenia in Older People recommended that both muscle mass and muscle function be evaluated for the diagnosis of sarcopenia [25]. However, it is difficult to evaluate muscle function in a retrospective study. Here we evaluated only muscle mass using preoperative CT images, which is assumed to be an objective and precise assessment of sarcopenia [21-23].

Regarding CT-based cut-off values, we were uncertain of the appropriate definition for the assessment of sarcopenia, and sex-specific cut-off values for sarcopenia for the Japanese population are lacking. Prado *et al.* reported the cut-off values for sarcopenia as L3 SMI ≤ 52.4 cm^2/m^2 for men and ≤ 38.5 cm^2/m^2 for women [19]. However, van Vledder *et al.* reported cut-off values of L3 SMI ≤ 43.75 cm^2/m^2 for men and ≤ 41.10 cm^2/m^2 for women [20]. Because the physique differs between Western and Japanese people, it is possible that we did not accurately evaluate sarcopenia using the cut-off values for Western populations. In the present study, we calculated the sex-specific cut-off values as L3 SMI ≤ 46.4 cm^2/m^2 for men and ≤ 37.6 cm^2/m^2 for women. Using these cut-off values, we found that the prevalence of sarcopenia in our HCC patient population was 46.5%.

With regard to the overall survival curves, we found a strong correlation between sarcopenia and overall survival (Fig. 2). The 5-year survival rate following hepatectomy was 58.2% among the patients with sarcopenia and 82.4% among those without sarcopenia, and the sarcopenic group had extremely poor survival. The molecular mechanism of sarcopenia is not fully understood. Skeletal muscle was recently identified as a secretory organ in which cytokines and other peptides are produced and released by muscle fibers [26]. Interleukin (IL)-6, an inflammatory cytokine released from skeletal muscle, affects liver metabolism, and high IL-6 levels are associated with an increased risk of HCC [27]. The activation of IL-6 might thus be related to sarcopenia and HCC progression.

Moreover, the levels of insulin-like growth factor 1 (IGF-1), an endocrine hormone produced primarily by the liver, are lower in older and sarcopenic patients [26,28]. Low IGF-1 levels are correlated with advanced clinicopathological parameters and poor survival in patients with HCC [29]. In the present study, sarcopenia was correlated with aging, advanced clinicopathological parameters, and poor survival. Further studies to elucidate the molecular mechanism between sarcopenia and HCC are needed.

Our multivariate analysis revealed that sarcopenia and ASA physical status of 3 or 4 were the only prognostic preoperative host factors related to overall survival after hepatectomy for HCC (Table 2). Similar to previous reports, tumor-specific factors such as multiple tumors and microvascular invasion, which is the T factor as per the guidelines of the Liver Cancer Study Group of Japan, were strong independent factors associated with survival [30,31], but tumor size and differentiation were not significantly associated with survival.

The results of a simple scoring system using preoperative risk factors are presented in Table 3. In this scoring system, we selected preoperative host predictors to establish a simple comprehensive system and excluded pathological factors that were determined only after surgery and difficult to accurately assess before surgery. Only 16 patients had both sarcopenia and a poor ASA status (the Risk 2 group). This group had the highest postoperative mortality rate and the lowest 3-year and 5-year survival rates (Fig. 3). At the same time, some patients (n = 118) had one risk factor (the Risk 1 group)—sarcopenia or poor ASA status—and the other patients (n = 120) had no preoperative factor (the Risk 0 group).

The ASA physical status is a subjective classification system and similar to the "eyeball test" [32], which detects frailty, but is an independent predictor of overall survival. However, sarcopenia is an objective assessment of frailty and is an important risk factor. Therefore, we were able to identify the potential risk for poor prognosis using a simple scoring system that represents both subjective and objective evaluations of host frailty.

Strategies for the assessment and management of sarcopenia including early preoperative detection and active interventions (such as nutritional treatment and exercise) may improve the postoperative outcomes for surgically high-risk patients with HCC. In several studies, combined nutrition and exercise interventions were the most effective strategies for sarcopenia management [33-36]. In the perioperative management of hepatectomy, in particular, perioperative nutritional support reduced postoperative complications [35], and early enteral nutrition had obvious advantages compared to parenteral nutrition [36]. However, no therapeutic algorithm for improving postoperative outcomes in patients with sarcopenia has been established. Future studies should be conducted to develop a method for identifying sarcopenia and establishing preoperative interventional treatments for sarcopenic patients.

Despite our important findings, this study has a few limitations. First, this was a retrospective, single-center study, and there may thus have been a potential selection bias for the patients for hepatectomy. Second, due to the retrospective design of the study we were unable to assess aspects of functional muscle status such as grip strength, walking speed, or levels of exhaustion. Third, the ASA physical status is subjective and sometimes evaluated differently by different anesthesiologists. Finally, we considered our cut-off values for SMI to be accurate for the evaluation of sarcopenia. Because there is no appropriate definition of CT-based assessment for sarcopenia in the Japanese, we used receiver operating characteristic curves to determine the cut-off values for SMI.

In conclusion, the result of our study indicates that in addition to a poor ASA physical status, sarcopenia is a unique, independent preoperative predictor of poor outcomes after hepatectomy. The assessment of sarcopenia and ASA status is an easy and feasible method. Furthermore, our new scoring system, which represents subjective and objective frailty, might help researchers develop comprehensive approaches for decision-making regarding surgical indications.

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