



Frailty predicts severe postoperative complications after elective colorectal surgery

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ABSTRACT

Background: We aim to clarify if frailty affects severe postoperative complications in elective colorectal surgery.

Methods: Consecutive 269 colorectal cancer patients older than 65 years undergoing curative surgery were enrolled in this study. The relevance of the frailty and sarcopenia to postoperative outcome was assessed. Clinical frailty (CF) was defined as clinical frailty scale (CFS) ≥ 4 . Sarcopenia was assessed by measuring skeletal muscle area using computed tomography.

Results: Seventy-eight patients (29%) had CF and 159 patients (59%) had sarcopenia. CF was significantly associated with older age ($P = 0.0008$), postoperative severe complications ($P = 0.001$), and postoperative in-hospital stay ($P < 0.0001$), although sarcopenia was not. Logistic regression analysis revealed that low anterior resection and CF were independent predictors of severe postoperative complications ($P = 0.038$ and $P = 0.001$, respectively).

Conclusion: CF, but not sarcopenia, is a robust predictor of severe postoperative complications in patients with colorectal cancer.

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Introduction

Frailty is a multidimensional, and heterogeneous syndrome associated with instability, and thus can be discriminated from disability or ageing alone.¹ Frailty is commonly measured using summative impairment lists and algorithms based on clinical judgment.^{1–4} Since the number of older patients requiring surgical treatment has been increasing with the development of surgery and anesthesia, preoperative risk assessments of such treatment for older patients needs to be properly determined in terms of both

curative and palliative care, the latter focused on maintaining quality of life. Frailty has been considered to be of great importance in predicting surgical outcomes in older patients.⁴

Sarcopenia, or the loss of muscle mass and coordination associated with aging is determined by various measures including total skeletal muscle at the level of the third spine, psoas density, and rectus femoris using computed tomography (CT), ultrasonography, and/or magnetic resonance imaging.^{5–10} Sarcopenia has been recognized as affecting vulnerability and is considered to reflect the frailty of patients.^{11,12} The clinical impact of sarcopenia on postoperative morbidity and mortality has been reported, but outcomes of such investigations depend on both the surgical procedure performed and the method by which sarcopenia is measured.^{5–10}

Colorectal cancer (CRC) is the third most common cancer worldwide and the fourth most common cause of death.¹³ Although surgical resection plays a major role in management of this disease, surgery is not without the serious complications of morbidity and mortality. In CRC patients, perioperative mortality ranges from 1% to 12% globally and occurs in <1% patients in

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Japan.^{14–16} Recently, the postoperative morbidity and mortality associated with CRC was linked not only with short-term outcomes, but also with worse long-term outcomes.^{17,18} Thus, the need to decrease severe postoperative complications is of great importance, not only based on the economic ramifications of such an initiative, but also from a prognostic perspective.

We have prospectively evaluated patients' frailty using a clinical frailty scale (CFS) to enable the selection of patients requiring extended perioperative rehabilitation to promote enhanced recovery after surgery (ERAS).² The aim of the current study was to assess the clinical impact of frailty on postoperative outcomes in patients with CRC. Since sarcopenia is already recognized as being predictive of surgical outcomes in patients with CRC,⁹ we compared the clinical impact of frailty to that of sarcopenia.

Patients and methods

Patients

This observational study included patients with histologically confirmed CRC who underwent elective surgery with curative intent in Saiseikai Kumamoto Hospital between January 2011 and August 2016. Patients with metastatic disease who underwent palliative procedures were excluded from the study. All patients received prophylactic antibiotics prior to induction of anesthesia as per hospital policy. All patients were cared for in accordance with the unit standardized ERAS protocol and clinical pathway; this included the administration of carbohydrate drinks preoperatively, early mobilization, and early enteral nutrition, with the avoidance of routine peritoneal and/or nasogastric drainage. On each postoperative day, patients were clinically assessed and had blood samples drawn, including for the assessment of serum C-reactive protein, as a standard procedure until being discharged. Patients' demographic and disease baseline characteristics, including their age, gender, height, weight, body mass index (BMI), comorbidities, and tumor-specific data including tumor location, size, and TNM staging according to the 2009 American Joint Committee on Cancer Staging were collected from medical records. The nutritional status of patients was also assessed using the prognostic nutritional index (PNI)¹⁹ which was calculated based on the serum albumin concentration and peripheral blood total lymphocyte count. The definitions of postoperative complications were determined by the Clavien-Dindo classification.²⁰ Grade \geq III in the Clavien-Dindo classification system is described as severe complication in this literature. Written informed consent was obtained from patients before surgery. This study was approved by the Human Ethics Review Committee of Saiseikai Kumamoto Hospital (Kumamoto, Japan).

Assessment of the CFS

Frailty was assessed according to CFS, which was based on clinical judgement.² Frailty classifications were based on a 1 to 7 numerical scale (and corresponding category description) as follows: CFS 1 (very fit), indicating patients were robust, active, energetic, highly-motivated, exercised regularly and exceptionally fit for their age; CFS 2 (well), without active disease, and less fit than patients in category CFS 1; CFS 3 (well with treated comorbid disease), indicating that disease symptoms were well managed compared with patients in category CFS 4; CFS 4 (apparently vulnerable), although independent, these people commonly complained of slowing down and/or had symptoms of disease; CFS 5 (mildly frail), patients with limited dependence on others for instrumental activities of daily living; CFS 6 (moderately frail), patients needed help with both instrumental and noninstrumental

activities of daily living; CFS 7 (severely frail), completely dependent on others for their activities of daily living, or terminally ill. In order to validate the utility and accuracy of the criteria, two independent observers (HO and OT) separately evaluated the CFS based on clinical information at admission for surgery. They were blinded to clinical and pathological data. In this study, the threshold for determining frailty was a CFS \geq 4.

CT image analysis and sarcopenia

Skeletal muscle area was retrospectively measured on CT images taken before surgery at the level of the third lumbar vertebra (L3) in the inferior direction with the patient in a supine position. Briefly, a three-dimensional image analysis system was employed to measure pixels using a window width of 30–150 HU to delineate the muscle compartments and compute the cross-sectional area of each in centimeters squared (cm^2). At the level of L3, the cross-sectional area of muscle (cm^2) computed from each image was normalized by the square of the height (m^2) to obtain the skeletal muscle index (cm^2/m^2). All measurements and calculations described above were performed by two trained examiners (HO and HT), 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 definition of sarcopenia proposed by Martin et al.²¹; sarcopenia was defined as a skeletal muscle index (SMI) = ([skeletal muscle area a L3]/[height]²) of $<43 \text{ cm}^2/\text{m}^2$ in men with a BMI of $<25 \text{ kg}/\text{m}^2$, $<53 \text{ cm}^2/\text{m}^2$ in men with a BMI of $\geq 25 \text{ kg}/\text{m}^2$, and $<41 \text{ cm}^2/\text{m}^2$ in women.

Statistics

Clinical characteristics were compared between groups using a chi-square analysis for noncontinuous variables and the *t*-test or the Wilcoxon test for continuous variables. Logistic regression analysis was performed by forward analysis including any significant parameters in univariate analysis to determine which clinical factors were associated with severe postoperative complications. Interobserver agreement for image findings of tumor was determined by calculating the κ coefficient. All *P*-values are two-sided, and $P < 0.05$ was considered statistically significant. All the analyses were performed using the commercial software (JMP Version 10[®], SAS Institute, Cary, NC, USA).

Results

Association of CFS with postoperative outcomes for CRC

In order to objectively evaluate CFS, the interobserver agreement of the images was measured by the kappa statistic. Kappa was calculated to be 0.69, suggesting that agreement was substantial. Seventy-eight patients (29.0%) were classified as frail. Frailty was significantly associated with older age ($P < 0.0001$), intraoperative bleeding ($P = 0.0015$), high incidence of both superficial and organ/space surgical site infection (SSI) ($P = 0.0376$), high incidence of severe complications ($P = 0.0010$), high hospital charges ($P < 0.0001$) and postoperative length of stay ($P < 0.0001$) (Table 1). However, frailty showed no significant correlation with BMI, sarcopenia and PNI.

Association of sarcopenia with postoperative outcomes for CRC

One hundred and fifty-nine patients (59.1%) had sarcopenia. Sarcopenia was significantly associated with female gender ($P < 0.0001$), high age ($P = 0.0008$), and high BMI ($P < 0.0001$). However, sarcopenia showed no correlation with postoperative

Table 1
Patient characteristics with or without frailty (n = 269).

Clinicopathological factors	Frailty (+)	Frailty (-)	P-value
	(n = 78)	(n = 191)	
Male	47 (60%)	120 (63%)	0.6938
Age ^a (years)	80 [65–89]	68 [65–84]	<.0001
BMI ^a	23 [14–35]	22 [15–34]	0.5415
Surgical procedure LAR	9 (12%)	24 (13%)	0.8158
Laparotomy	36 (46%)	63 (33%)	0.0437
Stage III/IV	15 (31%)	64 (29%)	0.7532
Experienced operator	47 (60%)	110 (58%)	0.6871
Operation time ^a (min)	262 [127–456]	259 [128–593]	0.5450
Bleeding ^a (ml)	100 [5–1980]	50 [5–1040]	0.0015
Sarcopenia	30 (38%)	79 (42%)	0.6364
Prognostic nutrition index ^a	44 [27–54]	47 [35–58]	0.0724
SSI total	20 (26%)	28 (15%)	0.0376
Anastomotic leakage	8 (10%)	12 (6%)	0.2731
Morbidity (Clavien-Dindo III/IV)	18 (23%)	16 (8%)	0.0010
Postoperative in-hospital stay	13 [7–64]	10 [6–61]	<.0001

SSI: surgical site infection.

^a Values are median [range].

outcomes such as the incidence of SSI, severe complications, high hospital charges and postoperative length of stay (Table 2).

CFS as an independent factor in predicting severe postoperative complications following CRC surgery

Clavien–Dindo III/IV complications were reported for 34 of 269 patients (12.6%) and included organ/space SSI (n = 5), anastomotic leakage (n = 18), gastrointestinal perforation (n = 3), intraperitoneal bleeding (n = 2), acute heart failure (n = 2), bowel obstruction (n = 2), hypercapnia (n = 1) and anastomotic bleeding (n = 1). No deaths were reported. The results of a univariate and multivariate analysis of frailty and other perioperative risk factors are shown in Table 3. The multivariate regression analysis identified the low anterior resection (LAR) surgical procedure, as well as frailty, as having the strongest association between the development of severe complications (odds ratios, 2.80 and 3.42, respectively; 95% confidential interval [CI], 1.06–6.92 and 1.62–7.29; P = 0.0383 and P = 0.0013). Although the total incidence of severe complications was significantly higher in the group of patients who were frail compared with the nonfrail group (P = 0.0010), the incidence of each severe complication was similar between the two groups (Table 4).

Table 2
Patient characteristics with or without sarcopenia (n = 269).

Clinicopathological factors	Sarcopenia (+)	Sarcopenia (-)	P-value
	(n = 159)	(n = 109)	
Male	81 (51%)	85 (78%)	<.0001
Age ^a (years)	77 [65–94]	72 [65–87]	0.0008
BMI ^a	21 [13–28]	24 [17–35]	<.0001
Surgical procedure LAR	12 (8%)	21 (20%)	0.0045
Laparotomy	60 (38%)	39 (36%)	0.7445
Stage III/IV	51 (32%)	28 (29%)	0.2577
Experienced operator	90 (57%)	66 (61%)	0.5199
Operation time ^a (min)	252 [128–601]	268 [127–593]	0.1266
Bleeding ^a (ml)	50 [5–1235]	50 [5–1980]	0.5140
Prognostic nutrition index ^a	47 [33–58]	48 [27–56]	0.8058
SSI	29 (18%)	19 (17%)	0.8655
Anastomotic leakage	11 (7%)	9 (7%)	0.6821
Morbidity (Clavien-Dindo III/IV)	21 (13%)	13 (12%)	0.7569
Postoperative in-hospital stay	11 [6–64]	11 [6–51]	0.8597

SSI: surgical site infection.

^a Values are median [range].

Table 3
Multivariate logistic regression analysis for severe postoperative complication.

Variable	Univariate	Multivariate	P-value
	P-value	Odds ratio [95% CI]	
Male	0.0643		
Age ^a ≥ 74 (years)	0.2583		
BMI ^a ≥ 22 (kg/m ²)	0.6200		
Surgical procedure LAR	0.0322	2.80 [1.06–6.92]	0.0383
Laparotomy	0.3440		
Stage III/IV	0.9952		
Experienced operator	0.7534		
Operation time ^a ≥ 263 (min)	0.5023		
Bleeding ^a ≥ 50 (g)	0.1824		
Sarcopenia	0.7569		
Frailty	0.0010	3.42 [1.62–7.29]	0.0013

^a Median values are used for the cut-off value.

Discussion

The results of this study indicate that frailty has a robust impact on the incidence of postoperative severe complications in patients with CRC. The vulnerability of patients to such complications may be easily identified by their general appearance at the first checkup; although, how to quantify that vulnerability has not yet been established. The CFS was central to our study; it is based on clinical judgement and as such we consider it is easy to use as well as powerfully correlated with surgical outcomes. A CFS of ≥4 was the threshold representative of frailty in our study. The basic concept of this premise is that patients who slow down requiring some support for dairy life or suffer from disease are a higher risk of severe postoperative complication after surgical treatment, irrespective of the medicines they are taking or previous conditions such as brain infarction, chronic kidney disease and/or heart failure. In addition, the analysis exploring the optimal cut-off value of CFS as a frail patient revealed that CFS of 4 was the most tightly correlated with postoperative outcome (data not shown). Correlation of the CFS with other established measurement tools, such as the frailty index based on clinical deficits has been previously confirmed.² We also confirmed that frailty determined by CFS is correlated with that determined by such frailty index with questionnaire sheet in the beginning of this study. Although we validated the objectivity by inter-observer analysis in this study, we appreciated that CFS is less quantitative than other frailty scores based on clinical questionnaires. Because frail patients are intensively intervened by rehabilitation both preoperatively and postoperatively in our institute, we have to assess how efficiently frail patients could be supported by the intensive rehabilitation based on such quantitative scores. We are now working on how CFS of ≥4 could be accurately scored by other tools or clinical questionnaires to improve the quantitative assessment of frail patients.

Table 4
Severe complication (Clavien-Dindo III/IV).

Clinicopathological factors	Frailty (+)	Frailty (-)	P-value
	(n = 78)	(n = 191)	
Total	18 (23%)	16 (8%)	0.0010
SSI (organ/space)	3 (4%)	2 (1%)	0.2961
Anastomotic leakage	8 (10%)	10 (5%)	0.9601
Gastrointestinal perforation	2 (3%)	1 (1%)	0.9602
Intraperitoneal bleeding	1 (1%)	1 (1%)	0.9005
Acute heart failure	2 (3%)	0	0.9828
Bowel obstruction	2 (3%)	0	0.9828
Hypercapnea	1 (1%)	0	0.2731
Anastomotic bleeding	1 (1%)	0	0.2731

SSI: surgical site infection.

Sarcopenia was not observed to correlate with any postoperative outcomes in this study. Recently, sarcopenia was associated with postoperative mortality in patients with gastrointestinal malignant diseases.^{7,9,22–25} However, there is no established parameter for vulnerability that can independently predict severe postoperative complications in patients undergoing surgery with curative intent for CRC. Although we assessed skeletal muscle using CT images, there are numerous methods by which sarcopenia can be assessed and surgical outcomes appear to be dependent on the basis of how sarcopenia is quantified. In patients with colorectal liver metastasis, sarcopenia defined by the total area of the psoas is associated with morbidity after a hepatectomy, whereas sarcopenia defined by the total muscle area at the level of the L3 vertebra was not correlated with postoperative complications.^{8,25} Since we did not assess sarcopenia using alternative methods, it is possible that sarcopenia was not properly determined in our patient cohort. Although we tried to explore the optimal cut-off value of muscle area, significant correlation between sarcopenia and severe postoperative complication was not eventually found in our cohort.

Given previous investigations focused on the impact of the nutritional index on postoperative complications,^{26,27} we speculated that the nutritional index might partially contribute to the diagnosis of frailty. If frail patients are impaired and do not obtain adequate nutrition, we would expect that nutritional support before or after surgery might be beneficial for them. However, there was no significant correlation between PNI and frail index. Frailty defined by CFS might be fundamentally discriminated from nutritional disorders and as such does not seem to be affected by perioperative nutritional interventions.

Since a robust correlation between frailty and morbidity was confirmed in our current observational study, we segue to our next concern about whether improvement of frailty before surgery could decrease morbidity. In patients undergoing a lung resection, preoperative exercise-based training was found to improve pulmonary function before surgery and reduces in-hospital length of stay and postoperative complications.²⁸ There are several major issues remaining before developing the preoperative exercise with the potential to improve frailty. Frailty is heterogeneous based on its root cause. Some patients have had an organ resected or locomotive disease or simply experience dementia as they age. Therefore, it is not easy to make a protocol of exercise applicable for any of such patients. Although it is challenging to overcome or reduce frailty within a limited duration, it is conceivable based on the current study that a decrease in frailty would affect a decrease in severe complications, independent of the surgical technique performed. We are now working on the establishment of protocol for preoperative exercise which needs the criteria to select frail patients who are tolerant for that.

In conclusion, frailty independently predicted severe postoperative complications in patients undergoing resection with curative intent, and as such, frailty should represent an important clinical consideration. Conceptually, frailty is accepted as being similar to sarcopenia, but based on the results of our study, it was not significantly correlated. Frail patients with CRC undergoing a resection with curative intent might have some unique requirements in order for their rehabilitation to be enhanced, and further interventions to explore perioperative rehabilitation needs should be addressed in the future.

Conflicts of interest

Authors have no conflicts of interest to disclose.

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References

- Hogan DB, MacKnight C, Bergman H, et al. Models, definitions, and criteria of frailty. *Aging Clin Exp Res*. 2003;15(3 Suppl):1–29. PubMed PMID: 14580013.
- Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ (Can Med Assoc J)*. 2005;173:489–495. PubMed PMID: 16129869. Pubmed Central PMCID: 1188185.
- Rolfson DB, Majumdar SR, Tsuyuki RT, et al. Validity and reliability of the edmonton frail scale. *Age Ageing*. 2006;35:526–529. PubMed PMID: 16757522.
- Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg*. 2010;210:901–908. PubMed PMID: 20510798.
- Gani F, Buettner S, Margonis GA, et al. Sarcopenia predicts costs among patients undergoing major abdominal operations. *Surgery*. 2016;160:1162–1171. PubMed PMID: 27302103.
- Nishigori T, Tsunoda S, Okabe H, et al. Impact of sarcopenic obesity on surgical site infection after laparoscopic total gastrectomy. *Ann Surg Oncol*. 2016;23(Suppl 4):524–531. PubMed PMID: 27380646.
- Wagner D, Buttner S, Kim Y, et al. Clinical and morphometric parameters of frailty for prediction of mortality following hepatopancreaticobiliary surgery in the elderly. *Br J Surg*. 2016;103:e83–e92. PubMed PMID: 26604018.
- Lodewick TM, van Nijnatten TJ, van Dam RM, et al. Are sarcopenia, obesity and sarcopenic obesity predictive of outcome in patients with colorectal liver metastases? *HPB*. 2015;17:438–446. PubMed PMID: 25512239. Pubmed Central PMCID: 4402055.
- Mueller N, Murthy S, Tainter CR, et al. Can sarcopenia quantified by ultrasound of the rectus femoris muscle predict adverse outcome of surgical intensive care unit patients as well as Frailty? A prospective, observational cohort study. *Ann Surg*. 2016;264:1116–1124. PubMed PMID: 26655919. Pubmed Central PMCID: 4907876.
- Sheetz KH, Waits SA, Terjimanian MN, et al. Cost of major surgery in the sarcopenic patient. *J Am Coll Surg*. 2013;217:813–818. PubMed PMID: 24119996. Pubmed Central PMCID: 3809011.
- Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol*. 2008;9:629–635. PubMed PMID: 18539529.
- Delmonico MJ, Harris TB, Lee JS, et al. Alternative definitions of sarcopenia, lower extremity performance, and functional impairment with aging in older men and women. *J Am Geriatr Soc*. 2007;55:769–774. PubMed PMID: 17493199.
- Global Burden of Disease Cancer C, Fitzmaurice C, Dicker D, et al. The global burden of cancer 2013. *JAMA Oncol*. 2015;1:505–527. PubMed PMID: 26181261. Pubmed Central PMCID: 4500822.
- Alves A, Panis Y, Mathieu P, et al. Postoperative mortality and morbidity in French patients undergoing colorectal surgery: results of a prospective multicenter study. *Arch Surg*. 2005;140:278–283. discussion 84. PubMed PMID: 15781793.
- Amemiya T, Oda K, Ando M, et al. Activities of daily living and quality of life of elderly patients after elective surgery for gastric and colorectal cancers. *Ann Surg*. 2007;246:222–228. PubMed PMID: 17667500. Pubmed Central PMCID: 1933572.
- Fielding LP, Phillips RK, Hittinger R. Factors influencing mortality after curative resection for large bowel cancer in elderly patients. *Lancet*. 1989;1:595–597. PubMed PMID: 2564119.
- Krurup PM, Nordholm-Carstensen A, Jorgensen LN, Harling H. Anastomotic leak increases distant recurrence and long-term mortality after curative resection for colonic cancer: a nationwide cohort study. *Ann Surg*. 2014;259:930–938. PubMed PMID: 24045445.
- Farid SG, Aldouri A, Morris-Stiff G, et al. Correlation between postoperative infective complications and long-term outcomes after hepatic resection for colorectal liver metastasis. *Ann Surg*. 2010;251:91–100. PubMed PMID: 19858702.
- Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nihon Geka Gakkai zasshi*. 1984;85:1001–1005. PubMed PMID: 6438478.
- Dindo D, Demartines N, Clavien PA. Classification of surgical complications – a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213. PubMed PMID: WOS:000222912600003. English.
- Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol*. 2013;31:1539–1547. PubMed PMID: 23530101.
- Fukuda Y, Yamamoto K, Hirao M, et al. Sarcopenia is associated with severe postoperative complications in elderly gastric cancer patients undergoing gastrectomy. *Gastric Cancer*. 2016;19:986–993. PubMed PMID: 26407875.
- Nishigori T, Okabe H, Tanaka E, et al. Sarcopenia as a predictor of pulmonary complications after esophagectomy for thoracic esophageal cancer. *J Surg Oncol*. 2016;113:678–684. PubMed PMID: 26936808.

24. Valero 3rd V, Amini N, Spolverato G, et al. Sarcopenia adversely impacts postoperative complications following resection or transplantation in patients with primary liver tumors. *J Gastrointest Surg*. 2015;19:272–281. PubMed PMID: 25389056. Pubmed Central PMCID: 4332815.
25. Peng PD, van Vledder MG, Tsai S, et al. Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. *HPB*. 2011;13:439–446. PubMed PMID: 21689226. Pubmed Central PMCID: 3133709.
26. Nozoe T, Kimura Y, Ishida M, et al. Correlation of pre-operative nutritional condition with post-operative complications in surgical treatment for oesophageal carcinoma. *Eur J Surg Oncol*. 2002;28:396–400. PubMed PMID: 12099649.
27. Nozoe T, Kohno M, Iguchi T, et al. The prognostic nutritional index can be a prognostic indicator in colorectal carcinoma. *Surg Today*. 2012;42:532–535. PubMed PMID: 22139087.
28. Sebjo Garcia R, Yanez Brage MI, Gimenez Moolhuyzen E, et al. Functional and postoperative outcomes after preoperative exercise training in patients with lung cancer: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg*. 2016;23:486–497. PubMed PMID: 27226400.