Applied nutritional investigation

Impact of sarcopenia on clinical outcomes after radical gastrectomy for patients without nutritional risk

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ABSTRACT

Objective: The aim of this study was to investigate the prevalence of sarcopenia in patients without nutritional risk and the association between sarcopenia and postoperative outcomes after radical gastrectomy in these patients.
Method: We conducted a study of non-nutritional risk patients with gastric cancer who underwent gastrectomy from August 2014 to December 2017 in two centers. Nutritional Risk Screening 2002 (NRS 2002) was used to evaluate the nutritional risk. Patients who with NRS 2002 score <3 were classified as having no nutritional risk and were included in the study. Demographic and perioperative data were gathered. Sarcopenia was diagnosed based on the European Working Group on Sarcopenia in Older People criteria. Univariate and multivariate analysis were performed to determine the association between preoperative risk factors and postoperative complications.
Results: In all, 545 patients were included, in which the prevalence of sarcopenia and postoperative complications was 7.3% and 21.1%, respectively. Sarcopenia was significantly associated with higher age, lower body mass index, lower handgrip strength, lower usual walking speed, longer postoperative hospital length of stay, and higher costs. Multivariate analysis of prognostic factors revealed that sarcopenia was an independent predictor (odds ratio, 2.330; 95% confidence interval, 1.132−4.796; *P* = 0.022] for postoperative complications. Male sex, diabetes, and preoperative anemia also were risk factors for postoperative complications.
Conclusion: Sarcopenia was a significant independent risk factor for postoperative complications after gastrectomy in patients without nutritional risk. Preoperative assessment and management of sarcopenia should be helpful for improving clinical outcomes for patients without nutritional risk.

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Introduction

Gastric cancer is the fourth most common malignancy and the second leading cause of cancer-related death in the world [1]. Owing to the cancer pain, dietary restriction, malabsorption, and chronic blood loss, many patients with gastric cancer have poor nutritional status [2]. Nutritional risk is closely associated with increased morbidity and mortality after surgery, such as prolonged hospital length of stay (LOS), increased surgical site infection, and increased readmission [2−6]. Currently, preoperative assessment of nutritional risk has been widely carried out in clinical practice and malnutrition has been considered a public health problem. Patients with nutritional risk acquire more attention and more

resource from clinical practice. Conversely, well-nourished patients are always ignored by surgeon.

Nutritional Risk Screening 2002 (NRS 2002) is a simple and reliable assessment tool of nutritional risk, which has been recommended to use in hospital patients by the European Society for Clinical Nutrition and Metabolism (ESPEN) [7]. Many studies have demonstrated that NRS 2002 can predict postoperative outcomes in patients who underwent major surgery [3,8]. A previous study demonstrated that sarcopenia and nutritional status are associated with postoperative complications after total gastrectomy [9]. In this study, 57.6% of the patients were without nutritional risk (NRS 2002 <3). However, for these patients, the presence of postoperative complications was still as high as 27.6%. Hence, it is necessary to further stratify preoperative risk in patients without nutritional risk.

Sarcopenia is a syndrome characterized by low muscle mass and low muscle function (strength or performance), which has been reported to be associated with negative clinical outcomes after colorectal, bladder, pancreatic, hepatic, and gastric surgery [10–13]. Most studies investigated the prevalence of sarcopenia and its outcomes in community-dwelling individuals and patients with malignancies, but sarcopenia has not been evaluated in patients without nutritional risk.

Considering the high prevalence of postoperative complications for patients without nutritional risk and the value of sarcopenia in the prediction of postoperative complications, we designed this study to investigate whether sarcopenia can well predict postoperative complications after gastrectomy for patients without nutritional risk.

Method and patients

This was a secondary analysis of the prospective data from a project investigating the association between nutrition and physical performance with clinical outcomes, which has been registered in Chinese Clinical Trial Registry (ChiCTR). Between August 2014 and December 2017, a total of 545 gastric cancer patients were included in this study in the First Affiliated Hospital of Wenzhou Medical University and Shanghai Tenth People's Hospital Affiliated to Tongji University. All the patients' nutritional status was assessed by research assistants using the NRS 2002 within the first 24 h after being hospitalized. Patients meeting the inclusion criteria contained had an NRS 2002 score <3; were ≥18 y of age; had preoperative abdominal computed tomography (CT) scans available for assessing sarcopenia; were able to complete all tests for muscle function; and agreed to take part in the study and signed the informed consent. Excluded patients were those with an NRS 2002 score ≥3; disagreed to join in this study; could not complete the muscle functional tests; and had cancer metastasis that could not be cured by radical surgery. All patients gave written informed approved by the ethics committee of the First Affiliated Hospital of Wenzhou Medical University and Shanghai Tenth People's Hospital Affiliated to Tongji University. All patients were informed about perioperative and intraoperative management.

Data collection

Data was gathered on patient characteristics like age, sex, height, weight, body mass index (BMI), preoperative comorbidity, the American Society of Anesthesiologists (ASA) physical status classification, plasma albumin concentration (<35 g/L, defined as hypoproteinemia), and hemoglobin concentration (<120 g/L for men and <110 g/L for women, defined as anemia). In addition, data were also recorded on surgery and anesthesia, such as surgical duration, tumor location, epidural use, laparoscopic-assisted surgery, type of resection, type of reconstruction, and combined resection. Histologic type was classified into depth of tumor invasion (T score), lymph node metastasis (N score), and stage and were described according to the third English edition of the Japanese Classification of Gastric Carcinoma [14]. The main postoperative outcome was postoperative complications (within 30 d after the operation). The second outcomes included postoperative mortality (within 30 d after the operation), hospital LOS, hospital costs, and readmissions within 30 d of discharge.

Postoperative complications assessment

The data and complications were documented independently by two surgeons. Some uncertain cases were solved by discussion. Complications classified as grade II or above according to the Clavien-Dindo classification were analyzed in this study [15]. Small bowel obstruction was diagnosed if one or more of the following criteria were met: patients developed signs, symptoms, and radiographic evidence of small bowel obstruction after evidence of return of gastrointestinal function, or mechanical intestinal obstruction was definitively confirmed by relaparotomy or contrast study [16]. In addition, delayed gastric emptying was mainly diagnosed by radiographic contrast techniques after eliminate mechanical obstruction [17]. Anastomotic leakage was diagnosed if one or both of the following criteria were met: methylene blue discharge from the peritoneal drains after an oral intake of methylene blue or extravasation of contrast material after an oral intake of water-soluble contrast material on CT scans [18].

NRS 2002 assessment

NRS 2002 was used to evaluate nutritional risk on the day patients were admitted to hospitals. The total NRS 2002 score was calculated from the severity of disease (score 0–3), the nutritional status (score, 0–3) and the age (score +1 for age >70 y). Patients were identified as having nutritional risk when NRS 2002 score was ≥3. Patients who did not have nutritional risk (NRS 2002 <3) were included in this study.

Sarcopenia assessment

Sarcopenia was defined as low muscle mass plus low muscle strength or low physical performance based on the European Working Group on Sarcopenia in Older People (EWGSOP) criteria [19]. The test of 6 m usual gait speed was performed twice and the mean value was taken to evaluate physical performance. The cutoff of usual gait speed was <0.8 m/s. Muscle strength was assessed by handgrip strength (HGS), which was measured by an electronic hand dynamometer (EH101; Camry, Guangdong Province, China). Patients were asked to use all their strength to grip the dynamometer with their dominant hand twice with 1-min rest between each measurement. The higher value of the two tests was taken. The cutoff of HGS was <26 kg for men and <18 kg for women.

Patients underwent enhanced abdominal CT as part of routine preoperative workup, and the preoperative CT within 1 mo was used to estimate muscle mass. The cross-sectional image at the L3 level of the lumbar vertebra was chosen to calculate the skeletal muscle mass. Skeletal muscle was identified and quantified by Houndsfield unit thresholds of −29 to +150. Total cross-sectional area of skeletal muscles at the L3 level was normalized to height (cm^2/m^2) to acquire the skeletal muscular mass indexes (SMIs). According to a previous large cohort study [20], the cutoff of SMI for men was <40.8 cm^2/m^2 and women was <34.8 cm^2/m^2.

Statistical analyses

Continuous data were presented as mean + standard deviation (SD) and categorical variables were presented as number. Pearson's χ^2 test or Fisher exact test were used to test for differences in categorical variables. Normally distributed continuous data were compared using the independent samples t test. Nonnormally distributed continuous data were compared with the Mann–Whitney U test. Potential risk factors associated with postoperative complications were examined using univariate and multivariate analyses. (Variables with a $P < 0.10$ were included in the multivariate logistic regression analysis; $P < 0.05$ was considered statistically significant). All statistical analyses were performed using SPSS version 22 (IBM Corp, Armonk, NY, USA).

Results

Patient characteristics

Of the 545 eligible patients, 40 (7.3%) were categorized into the sarcopenia group and 505 (92.7%) into the non-sarcopenia group. Patient demographics and clinical data are shown in Table 1. Population characteristics are presented as number for categorical variables and mean with SD for continuous variables. The mean age of the cohort was 62.6 y and was predominantly male (76.7%). The proportion of female patients was higher in the sarcopenia group than non-sarcopenia group (37.5% versus 22.2%; $P = 0.027$). Compared with patients in the non-sarcopenia group, patients in the sarcopenia group were older (70.6 versus 61.9 y; $P < 0.001$), lower HGS (19.5 versus 31.2 kg; $P < 0.001$) and lower BMI (21.6 vs 23.5 kg/m²; $P < 0.001$). In addition, postoperative hospital LOS and hospital cost were significantly higher in the sarcopenia group. With respect to history of hypertension and diabetes, ASA grade, tumor

Table 1
Patient demographic and clinical characteristics

Characteristic	Total (N = 545)	Sarcopenic (n = 40)	Nonsarcopenic (n = 505)	P-value
Age (y), mean (SD)	62.62 (10.53)	70.63 (11.13)	61.93 (10.20)	<0.001*
Sex				0.027*
Male	418	25	393	
Female	127	15	112	
BMI (kg/m^2)	23.37 (2.90)	21.62 (2.56)	23.50 (2.87)	<0.001*
ASA				0.248
I	147	10	137	
II	323	21	302	
III	75	9	66	
Hypertension				0.670
No	384	27	357	
Yes	161	13	148	
Diabetes				0.115
No	484	32	452	
Yes	61	8	53	
Albumin (g/L), mean (SD)	39.02 (4.29)	35.55 (4.46)	39.29 (4.16)	<0.001*
Hemoglobin (g/L), mean (SD)	124.90 (26.03)	107.48 (21.10)	126.28 (25.90)	<0.001*
Handgrip strength (kg), mean (SD)	30.32 (9.26)	19.50 (6.30)	31.18 (8.91)	<0.001*
Gait speed (m/s), mean (SD)	1.04 (0.20)	0.87 (0.21)	1.06 (0.19)	<0.001*
Previous abdominal surgery				0.653
No	482	34	448	
Yes	63	6	57	
Operation method				0.915
Open	350	26	324	
Laparoscopy	195	14	181	
Epidural anesthesia				0.115
No	171	17	154	
Yes	374	23	351	
Type of reconstruction				0.515
Billroth I	233	15	218	
Billroth II	112	11	101	
Roux-en-y	200	14	186	
Type of resection				0.915
Subtotal gastrectomy	372	27	345	
Total gastrectomy	173	13	160	
Tumor location				0.984
Proximal location	56	4	52	
Medium third location	130	10	120	
Distal location	359	26	333	
Surgical duration (min), mean (SD)	200.81 (50.29)	193.58 (43.98)	201.39 (50.76)	0.352
TNM stage				0.064
I	218	9	209	
II	127	12	115	
III	200	19	181	
Readmissions				0.998
No	511	37	474	
Yes	34	3	31	
Postoperative complications				0.002*
No	430	24	406	
Yes	115	16	99	

ASA, American Society of Anesthesiologists; BMI, body mass index; SMI, skeletal muscle index
Values given are number of patients unless indicated otherwise
*Statistically significant ($P < 0.05$).

stage, and previous abdominal surgery, the two groups did not differ significantly.

Complication and readmission

Postoperative complications (grade ≥2) according to the Clavien-Dindo classification were reported in 115 (21.1%) of patients. Of these complications, 35 were classified as grade 3 or higher. The details of postoperative complications are listed in Table 2. The prevalence of postoperative complications of the sarcopenia patients was significantly higher than that of the non-sarcopenia patients (40% versus 19.6%; $P = 0.002$). Thirty-four (6.2%) patients were readmitted to the hospital within 30 d: 31 (6.1%) from the

non-sarcopenia group and 3 (7.5%) from the sarcopenia group. There was no significant differentiation of the incidence of readmission between the two groups. Only one person from the non-sarcopenia group died within 30 d of surgery because of heart failure. No deaths were reported in the sarcopenia group.

Univariate and multivariate analysis

Univariate analysis was performed to evaluated the potential associations of postoperative complications with age, sex, BMI, anemia, hypoalbuminemia, previous abdominal surgery, and pathologic characteristics. Risk factors for postoperative complications are shown in Table 3, and all factors with $P<0.1$ were further analyzed

Table 2
Types of complications

Complication types	Total (N = 545)	Sarcopenic (n = 40)	Nonsarcopenic (n = 505)
Grade II	80	11	69
Delayed gastric emptying	4	1	3
Intra-abdominal hemorrhage	7	1	6
Intra-abdominal infection	15	0	15
Pneumonia	11	2	9
Anastomotic leakage	9	1	8
Malnutrition	2	1	1
Small bowel obstruction	6	3	3
Lymphatic fistulas	2	0	2
Wound infection	5	0	5
Venous thrombosis	5	1	4
Pulmonary embolism	2	0	2
Pulmonary atelectasis	3	0	3
Liver dysfunction	2	0	2
Others	7	1	6
Grade III	25	2	23
Intra-abdominal hemorrhage	6	0	6
Hydrothorax	3	1	2
Pneumonia	2	0	2
Seroperitoneum	6	0	6
Delayed gastric emptying	3	0	3
Anastomotic leakage	4	0	4
Small bowel obstruction	1	1	0
Grade IV	9	3	6
Pulmonary embolism	2	1	1
Pulmonary atelectasis	2	1	1
Heart failure	1	0	1
Respiratory failure	3	1	2
Multiple organ failure	1	0	1
Grade V	1	0	1
Death	1	0	1
Total, n (%)	115 (21.1)	16 (40)	99 (19.6)

in the multivariate analysis. Multivariate analysis showed that sex (male or female; odds ratio [OR], 2.252; 95% confidence interval [CI], 1.256–4.038), diabetes (OR, 2.462; 95% CI, 1.354–4.478), preoperative anemia (OR, 2.354; 95% CI, 1.517–3.652), and sarcopenia (OR, 2.330; 95% CI, 1.132–4.796) were significantly associated with postoperative complications (Fig. 1).

Discussion

The present study investigated the association between sarcopenia and postoperative outcomes after radical gastrectomy in patients with no nutritional risk. Sarcopenia was diagnosed following the EWGSOP criteria [19], and nutritional risk was assessed with NRS 2002 [21]. In the present study, the overall prevalence of postoperative complications for non-nutritionally at-risk patients with gastric cancer was 21.1%. The results of multivariate analysis showed that sarcopenia was an independent predictor of postoperative complications for patients not at nutritional risk. Among this cohort, the prevalence of postoperative complications for patients with sarcopenia was 40%, significantly higher than the 19.6 for patients without sarcopenia.

In clinical practice, patients at nutritional risk are generally considered as being at high surgical risk. Therefore, detailed preoperative assessment and nutritional support would be planned for them. However, patients not at nutritional risk received relatively less preoperative assessment and were considered unsuitable for parental or enteral nutritional support. The present study

demonstrated that 21.1% of the patients not at nutritional risk had postoperative complications after gastrectomy. The result was similar with a previous study [9]. In a study by Guo et al., the prevalence of postoperative complications for non-nutritionally at-risk patients with gastric cancer was 13.8% and lower than our results [22]. This may be due to the heterogeneity of the patient cohorts and the different methods used to assess postoperative complications. In another study of patients with colorectal cancer, Schwegler et al. found that the prevalence of postoperative complications was 39.8% for patients an NRS score <3 after surgery [3]. Hence, as shown by the present study and several previous studies, the incidence of postoperative complications for patients not at nutritional risk is still high and should not be ignored by surgeons.

The high prevalence of postoperative complications for patients not at nutritional risk indicates that using only the NRS 2002 to predict postoperative complications is insufficient. Weight loss and BMI are two of the major components of NRS 2002 scores, whereas the definition of sarcopenia is mainly based on muscle mass and physical function. Weight loss is a relatively subjective parameter and can be affected by the hydroelectrolytic disorders. BMI did not distinguish between fat mass and fat-free mass (FFM). Patients can be diagnosed as sarcopenia with normal BMI because of the loss of lean body mass and the accumulation of fat mass. This is called *sarcopenia obesity* [23]. Skeletal muscle has been recognized as the most clinically relevant component of body mass and can be accurately assessed by CT and magnetic resonance scan. The ESPEN consensus for malnutrition in 2015 also emphasized the importance of assessing FFM, which indicates the significance of the assessment of skeletal muscle mass [7]. Thus, sarcopenia can be a good parameter for preoperative assessment in addition to NRS 2002 score.

Given the clinical significance of sarcopenia, it has been included in the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) [24]. Although there is still no generally accepted guidelines for the treatment of sarcopenia, many studies have reported that it can be improved by resistance exercise and nutritional intervention [25–27]. A study by Yamamoto et al. found that preoperative exercise and nutritional support program can reduce sarcopenia and improve postoperative outcome in elderly patients with sarcopenia and gastric cancer [27]. Furthermore, a systematic review and meta-analysis also showed some positive effects of exercise and nutritional interventions for treating sarcopenia in older adults [28].

In addition to sarcopenia, we also found that sex, diabetes, and preoperative anemia also were significantly associated with postoperative complications according to the results of multivariate analysis. There are considerable evidences of the association between preoperative anemia and surgical morbidity and mortality. In a large cohort study, preoperative anemia was an independent risk factor for mortality in multivariate analysis [29]. Preoperative diabetes also has been reported to be associated with poor clinical outcomes [30]. A recent study showed that preoperative diabetes management can improve clinical outcomes after elective surgery [31]. Hence, for surgical patients, anemia and diabetes can be improved by adequate preoperative management and are not contraindications to surgery.

The present study had several limitations. First, we only analyzed the immediate (30 d) postoperative outcomes. Further investigation is needed to evaluate the association between sarcopenia and outcomes that occur after a longer postoperative period for patients without nutritional risk after gastrectomy. Second, this was an observational study. We did not give special interventions

Table 3
Univariate analysis of factors associated with postoperative complications

Factor	Complications (n = 115)	No complications (n = 430)	Odds ratio	95% CI	P-value
Age (y)					
<65	51	252			
≥65	64	178	1.777	1.173–2.690	0.006*
Sex					
Male	98	320	1.982	1.133–3.464	0.015*
Female	17	110			
BMI (kg/m²)					
<24	64	265			
≥24	51	216	1.280	0.844–1.940	0.245
ASA					0.066
I	25	122			
II	71	252			
III	23	52			
Hypertension					
No	72	312			
Yes	43	118	1.579	1.024–2.435	0.038*
Diabetes					
No	93	391			
Yes	22	39	2.372	1.342–4.191	0.002*
Anemia†					
No	60	314			
Yes	55	116	2.481	1.625–3.789	<0.001*
Hypoproteinemia‡					
No	93	362			
Yes	22	68	1.259	0.740–2.144	0.395
Sarcopenia					
No	99	406			
Yes	16	24	2.734	1.400–5.341	0.002*
TNM stage					0.528
I	42	176			
II	31	96			
III	42	158			
Tumor location					0.172
Proximal location	14	42			
Medium third location	20	110			
Distal location	81	278			
Laparoscopic surgery					
No	84	266			
Yes	31	164	0.599	0.380–0.944	0.026*
Previous abdominal surgery					
No	100	382			
Yes	15	48	1.194	0.642–2.219	0.575
Epidural anesthesia					
No	28	143			
Yes	87	287	1.548	0.967–2.479	0.067
Surgical durations					
<210min	64	250			
≥210min	50	178	1.097	0.723–1.665	0.663
Combined organ resection					
No	102	408			
Yes	13	22	2.364	1.151–4.852	0.016*
Type of reconstruction					0.150
Billroth I	42	191			
Billroth II	22	90			
Roux-en-Y	51	149			
Type of resection					
Subtotal gastrectomy	73	299			
Total gastrectomy	42	131	1.313	0.853–2.022	0.215

ASA, American Society of Anesthesiologists; BMI, body mass index; TNM, tumor node metastasis.
*Statistically significant ($P < 0.05$).
†Hemoglobin concentration <120 g/L for men and <110 g/L for women was defined as anemia.
‡Plasma albumin concentration <35 g/L was defined as hypoproteinemia.

to the sarcopenia patients to investigate whether preoperative management of sarcopenia can improve postoperative outcomes. To address that question, a well-designed randomized controlled trial is necessary in the future.

Conclusion

The present study demonstrated that there was a high incidence of postoperative complications for patients without
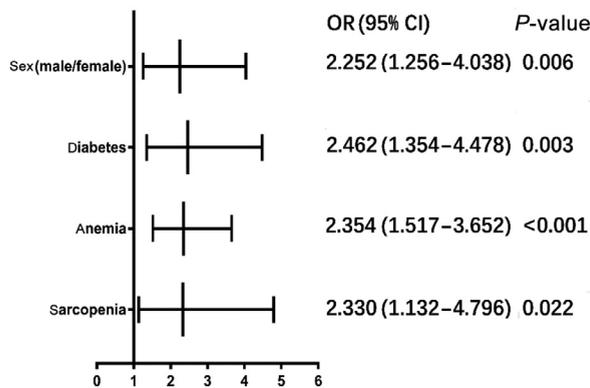
Fig. 1. Multivariate logistic regression analysis of factors associated with postoperative complications.

nutritional risk who underwent gastrectomy for gastric cancer. Sarcopenia is an independent risk factor for postoperative complications for these patients. The present study indicated that it is essential to assess sarcopenia before surgery for patients with gastric cancer patients who are not at nutritional risk.

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