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Original Article

Muscle Quality Predicts Outcomes after Surgery for Early-Stage Non–Small-Cell Lung Cancer

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Purpose: This study investigated the impact of skeletal muscle quality on the outcomes of patients undergoing surgery for early-stage non–small-cell lung cancer (NSCLC).
Methods: A total of 98 patients with pathological stage I–II NSCLC who underwent lobectomy or segmentectomy were retrospectively analyzed. Along with skeletal muscle quantity, muscle quality was evaluated by intramuscular adipose tissue content (IMAC) at the first lumbar vertebral level; a higher IMAC indicates lower skeletal muscle quality. Patients were divided into two groups according to the gender-specific quartiles of IMAC, and the prognostic impact of IMAC was investigated.
Results: No significant differences in the body and skeletal mass indices, which indicate skeletal muscle quantity, were observed between patients with high and those with normal IMAC. Patients with high IMAC (n = 23) showed a significantly poorer prognosis in overall and disease-specific survivals than those with normal IMAC (n = 75; P <0.001 and P = 0.048, respectively). In a bivariate analysis that included other clinicopathological factors, a high IMAC was independently associated with worse overall survival.
Conclusion: The skeletal muscle quality evaluated by IMAC could be used to predict survival risk after surgery for early-stage NSCLC.

Keywords: non–small-cell lung cancer, sarcopenia, muscle quality, muscle quantity

Introduction

Lung cancer is a leading cause of cancer-related death worldwide.[1] Surgery is the standard treatment strategy for early-stage lung cancer, and many previous studies have reported prognostic factors after surgery that are associated with tumor characteristics and patient background.[2]

Sarcopenia, which is characterized by a progressive and generalized loss of skeletal muscle and strength, was first reported in 1997.[3] This loss is caused by various mechanisms, such as aging-related changes, inadequate nutrition/malabsorption, neurodegenerative disease, physical inactivity, insulin resistance, and cachexia.[3,4] In recent years, sarcopenia has been identified as an important prognostic factor after surgery for lung cancer.[5,6] Moreover, we have easily been able to assess the body composition in terms of muscle mass and adipose tissue due to the greater availability of imaging systems such as computed tomography (CT), and several studies have reported that skeletal muscle quality evaluated by measuring intramuscular adipose tissue content (IMAC) is related to poor postoperative outcomes in patients with abdominal cancer or cardiovascular disease.[7–9]

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To the best of our knowledge, there are no reports on the association between skeletal muscle quality and postoperative outcomes in patients with lung cancer. This study investigated the impact of muscle quality as well as quantity on outcomes in patients undergoing surgery for early-stage non–small-cell lung cancer (NSCLC).

Materials and Methods

The Institutional Review Board (IRB) approved this retrospective review and waived the need for obtaining informed consent from patients (IRB number: 2020-10).

Patient population

The medical records of 175 consecutive patients who underwent surgery at the National Hospital Organization Higashihiroshima Medical Center between April 2012 and March 2016 were evaluated. Patients who underwent wedge resection, had other histological types except for NSCLC, had greater than pathological stage III lung cancer, underwent preoperative therapy, had incompletely resected tumors (R1), and were lost to follow-up were excluded, and the remaining 98 patients with pathological stage I–II NSCLC who underwent curative surgery via lobectomy or segmentectomy without induction therapy were evaluated (**Supplementary Fig. 1**; all supplementary files are available online.).

Preoperative staging was determined through high-resolution computed tomography (HRCT) and 18-fluoro-2-deoxyglucose positron emission tomography/CT. Tumors were staged according to the *TNM Classification of Malignant Tumors*, 7th edition.[10] Pathological diagnosis was based on the *WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart*.[11]

HRCT imaging

We performed preoperative plain chest CT at the first lumbar vertebral level to assess the quality and quantity of the skeletal muscles (**Figs. 1a** and **1b**). All patients underwent chest CT within 1 month before surgery.

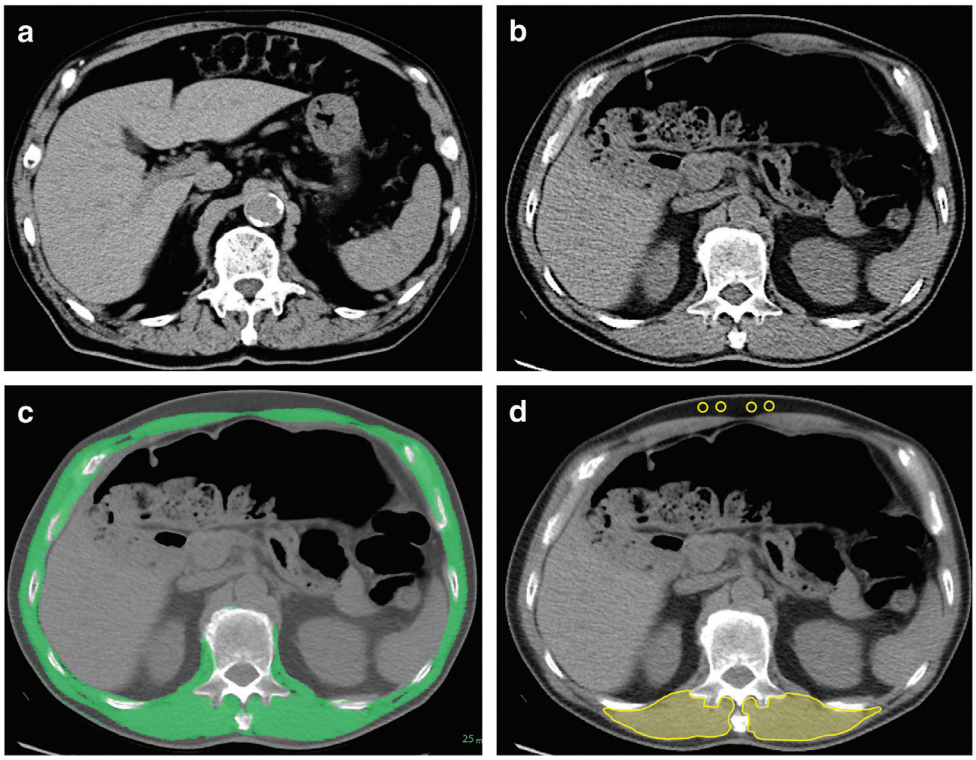

Fig. 1 Preoperative skeletal muscle quality and quantity were evaluated at the first lumbar vertebral level using CT. (**a**) Representative example of low quality and normal quantity of skeletal muscle. (**b**) Representative example of normal quality and quantity of skeletal muscle. (**c**) Skeletal muscle mass of the paraspinal and chest–abdominal wall muscles was quantified using an attenuation value of −29 to −150 HU (green area). (**d**) To calculate IMAC, the CT attenuation values of the paraspinal muscles (yellow area) and subcutaneous fat (four yellow small circles) were examined. CT: computed tomography; HU: Hounsfield unit; IMAC: Intramuscular adipose tissue content

The truncal muscle area was quantified using the SYNAPSE VINCENT (Fujifilm Medical, Tokyo, Japan) image analysis software, and attenuation values from −29 to 150 Hounsfield unit (HU) were used.

The skeletal muscle quantity was evaluated using the skeletal mass index (SMI), which was calculated as the ratio of the cross-sectional areas of truncal muscle (cm^2) to the squared height of the patient (m^2). The truncal muscles comprised the paraspinal and chest–abdominal wall muscles (**Fig. 1c**). Skeletal muscle quality was evaluated by IMAC and was calculated preoperatively as the ratio of the CT attenuation value of the paravertebral muscles, measured by tracing the preoperative CT images (HU), to the subcutaneous fat (HU) (**Fig. 1d**). CT values were measured for the region of interests (ROIs) of four circles on subcutaneous fat. The mean values of these four ROIs were used as the ROI to assess the subcutaneous fat. A higher IMAC indicated a higher amount of adipose tissue within the skeletal muscle, and hence, indicated lower skeletal muscle quality.

Follow-up evaluation

All patients were followed up from the day of the surgery. For the first 2 years, postoperative follow-up comprised a physical examination and chest radiograph every 3 months and a chest and abdominal CT examination every 6 months. In subsequent years, physical examinations and chest radiographs were conducted every 6 months, and chest and abdominal CT scans were performed every year.

Cutoff values of IMAC and SMI

The cutoff values of SMI and IMAC were determined separately for men and women. Patients were divided into two groups according to the gender-specific quartiles of IMAC (upper quartiles, −0.38 and −0.34 for men and women, respectively) or SMI (lower quartiles, 31.9 and 28.0 cm^2/m^2 for men and women, respectively). A high IMAC, or low muscle quality, was defined as greater than or equal to the IMAC cutoff value; similarly, a low SMI, or low muscle quantity, was defined as less than or equal to the SMI cutoff value. The prognosis of patients with a high IMAC or low SMI was compared with that of those with normal IMAC or SMI.

Statistical analysis

Normally distributed continuous variables were reported as mean (standard deviation) and compared using the Student's-t test. Nonnormally distributed continuous variables were reported as median and interquartile range (IQR) and compared using the Wilcoxon rank-sum test. Categorical variables were compared using the chi-squared or Fisher's exact tests and were used to compare frequencies. Overall survival (OS) was defined as the time from surgery to death from any cause. Disease-specific survival (DSS) was defined as the time from surgery to death from lung cancer. Survival data were estimated using the Kaplan–Meier method and compared using a log-rank test.

The prognostic significance of the IMAC for OS and DSS was assessed using univariate and bivariate analyses with the Cox proportional hazards model adjusted for the clinicopathological factors of age, sex, body mass index (BMI), smoking history, albumin, neutrophil-to-lymphocyte ratio, prognostic nutritional index (PNI), modified Glasgow prognostic score (mGPS), carcinoembryonic antigen (CEA), tumor location, surgical procedure, histological type, lymphovascular invasion, pleural invasion, pathological stage, and SMI. PNI and mGPS were calculated as previously described.[12,13] The statistical analysis was performed using JMP version 14 (SAS Institute, Cary, NC, USA). A P-value of <0.05 was considered statistically significant.

Results

Patient characteristics

Table 1 summarizes the characteristics of the 98 patients. Patients with high IMAC were older (P = 0.039). Nineteen (82.6%) patients with high IMAC and 55 (73.3%) with normal IMAC were aged ≥65 years. No significant differences in BMI ($kg/height^2$) and SMI ($area/height^2$) were observed between patients with high and normal IMAC.

Prognosis after surgery for lung cancer by IMAC or SMI

The median follow-up duration was 59 months. Deaths were observed in six (26.1%) patients with high IMAC and three (4.0%) with normal IMAC. Regarding the cause of death, deaths due to primary NSCLC were observed in three (13.0%) patients with high IMAC and three (4.0%) with normal IMAC. Furthermore, deaths due to other diseases were observed in three (13.0%; two aspiration pneumonia and one interstitial pneumonia) patients with high IMAC and none with normal IMAC.

Table 1 Characteristics of patients classified according to the IMAC

Variables	Value		*P*-value
	Normal IMAC (n = 75)	High IMAC (n = 23)	
Age (years), mean ± SD	67.4 ± 10.1	72.1 ± 7.2	0.039
Sex, n (%)			1.0
Male	39 (52.0)	12 (52.2)	
Female	36 (48.0)	11 (47.8)	
BMI (kg/m^2), median (IQR)	22.3 (20.1–24.8)	24.0 (21.6–25.9)	0.063
Smoking, n (%)			
Yes	39 (52.0)	13 (56.5)	0.81
Diabetes mellitus, n (%)	12 (16.0)	4 (17.4)	1.0
Interstitial pneumonia, n (%)	2 (2.7)	1 (4.4)	0.56
FEV_1 (L), median (IQR)	2.26 (1.85–2.62)	2.27 (1.92–2.56)	0.82
VC (L), median (IQR)	3.16 (2.55–3.60)	3.01 (2.58–3.44)	0.37
Alb (g/dL), median (IQR)	4.2 (3.9–4.5)	4.1 (3.9–4.4)	0.25
NLR, n (%)			0.18
≥3	21 (28.0)	3 (13.0)	
<3	54 (72.0)	20 (87.0)	
PNI, n (%)			0.45
≤40	22 (29.3)	9 (39.1)	
>40	53 (70.7)	14 (60.9)	
mGPS, n (%)			0.26
0	64 (85.3)	22 (95.7)	
1	8 (10.7)	0 (0)	
2	3 (4.0)	1 (4.4)	
CEA (ng/mL), median (IQR)	2.6 (1.7–3.8)	2.6 (1.8–3.8)	0.74
Nodule location, n (%)			0.38
Right upper lobe	22 (29.3)	10 (43.5)	
Right middle lobe	4 (5.3)	0 (0)	
Right lower lobe	19 (25.3)	5 (21.8)	
Left upper lobe	20 (26.7)	3 (13.0)	
Left lower lobe	10 (13.3)	5 (21.7)	
Surgical procedure, n (%)			0.60
Segmentectomy	19 (25.3)	7 (30.4)	
Lobectomy	56 (74.7)	16 (69.6)	
Histological type, n (%)			0.52
Adenocarcinoma	64 (85.3)	18 (78.3)	
Others	11 (14.7)	5 (21.7)	
Pleural invasion, n (%)			0.75
Present	11 (14.7)	4 (17.4)	
Vascular invasion, n (%)			0.61
Present	26 (34.7)	6 (26.1)	
Lymphatic invasion, n (%)			0.58
Present	17 (22.7)	7 (30.4)	
Pathological stage, n (%)			0.63
Stage IA	50 (66.7)	13 (56.5)	
Stage IB	14 (18.7)	5 (21.7)	
Stage IIA	5 (6.7)	3 (13.0)	
Stage IIB	6 (8.0)	2 (8.7)	
Adjuvant therapy, n (%)	25 (33.3)	8 (34.8)	1.0
SMI, n (%)			1.0
Low	18 (24.0)	5 (21.7)	
Normal	57 (76.0)	18 (78.3)	

Alb: albumin; BMI: body mass index; CEA: carcinoembryonic antigen; FEV_1: forced expiratory volume in 1 second; HR: hazard ratio; IMAC: intramuscular adipose tissue content; IQR: interquartile range; mGPS: modified Glasgow prognostic score; NLR: neutrophil-to-lymphocyte ratio; PNI: prognostic nutritional index; SD: standardized difference; SMI: skeletal muscle mass index; VC: vital capacity

In addition, recurrences were observed in four (17.4%) patients with high IMAC and six (8.0%) with normal IMAC.

The OS rate was significantly lower in patients with high IMAC (n = 23; 5-year OS, 82.4%; 95% CI, 61.3–93.2) than in patients with normal IMAC (n = 75; 5-year OS, 97.3%; 95% CI, 90.0–99.3; P <0.001; **Fig. 2a**). Similarly, the OS rate was significantly lower in patients with low SMI (n = 23; 5-year OS, 82.6%; 95% CI, 61.8–93.3) than in patients with normal SMI (n = 75; 5-year OS, 97.3%; 95% CI, 89.9–99.3; P = 0.022; **Fig. 2b**). According to the pathological stage, the OS rate was significantly lower in patients with high IMAC (n = 18; 5-year OS, 88.9%; 95% CI, 64.8–97.2) than in patients with normal IMAC (n = 64; 5-year OS, 98.4%; 95% CI, 89.7–99.8; P = 0.004; see **Supplementary Fig. 2a**) among patients with pathological stage I NSCLC. Similarly, the OS rate was also significantly lower in patients with high IMAC (n = 5; 5-year OS, 60.0%; 95% CI, 20.0–90.0) than in patients with normal IMAC (n = 11; 5-year OS, 90.9%; 95% CI, 56.1–98.7; P = 0.046; see **Supplementary Fig. 2b**) among patients with pathological stage II NSCLC. The DSS rate was significantly lower in patients with high IMAC (n = 23; 5-year DSS, 86.5%; 95% CI, 65.4–95.6) than in patients with normal IMAC (n = 75; 5-year DSS, 97.3%; 95% CI, 90.0–99.3; P = 0.048; **Fig. 3a**). Similarly, the DSS rate was significantly lower in patients with low SMI (n = 23; 5-year DSS, 87.0%; 95% CI, 66.5–95.7) than in patients with normal SMI (n = 75; 5-year DSS, 97.3%; 95% CI, 90.0–99.3; P = 0.013; **Fig. 3b**).

Risk factors for poor survival in patients undergoing surgery for lung cancer

The results of the univariate analysis for OS and DSS are shown in **Supplementary Table 1** and those of the bivariate analysis are shown in **Table 2**. In univariate analysis, a high IMAC (hazard ratio [HR] 13.6; 95% CI, 3.01–96.0; P <0.001), low SMI (HR 4.15; 95% CI, 1.09–16.9; P = 0.049), and pleural invasion (HR 6.26; 95% CI, 1.53–24.0; P = 0.013) were significantly associated with worse OS. On the other hand, low SMI (HR 6.51; 95% CI, 1.26–47.1; P = 0.026), pleural invasion (HR 14.1; 95% CI, 2.73–103; P = 0.002), lymphovascular invasion (HR 7.82; 95% CI, 1.26–150; P = 0.026), and mGPS (HR 7.73; 95% CI, 1.42–42.0; P = 0.020) were significantly associated with worse DSS. We determined the prognostic significance of IMAC using bivariate analysis. In bivariate analysis, a high IMAC was independently associated with worse OS when adjusted for all other clinicopathological factors, including SMI (P <0.001). However, IMAC was not a prognostic factor for DSS when adjusted for age (P = 0.082), sex (P = 0.077), smoking history (P = 0.079), albumin (P = 0.11), PNI (P = 0.11), CEA (P = 0.078), tumor location (P = 0.063), surgical procedure (P = 0.078), histological type (P = 0.073), lymphovascular invasion (P = 0.59), pleural invasion (P = 0.093), pathological stage (P = 0.11), and SMI (P = 0.057).

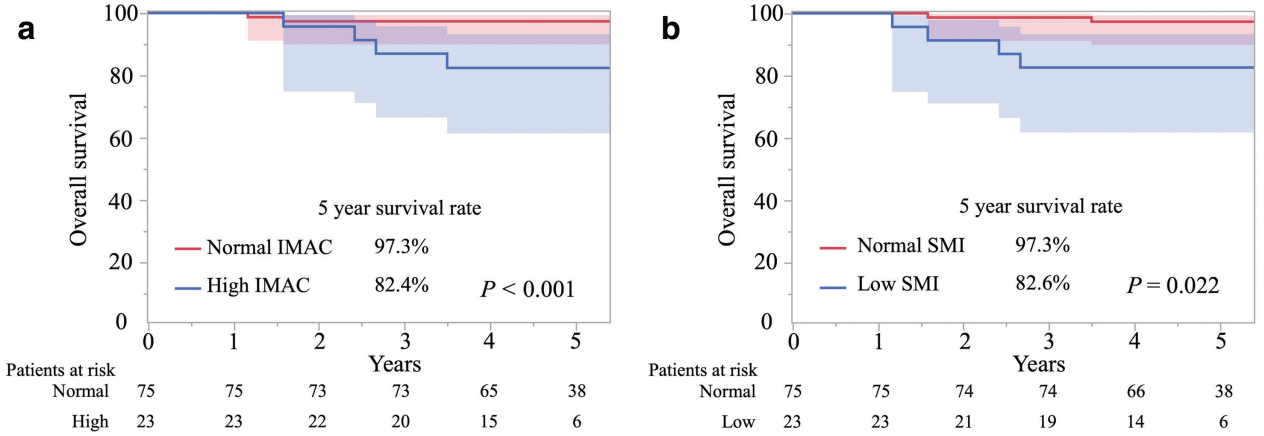

Fig. 2 OS curves of patients classified according to the IMAC or SMI criteria. (**a**) In all cohorts, 5-year OS was 97.3% (95% CI, 90.0–99.3) in patients with normal IMAC and 82.4% (95% CI, 61.3–93.2) in patients with high IMAC (P <0.001). (**b**) In all cohorts, 5-year OS was 97.3% (95% CI, 89.9–99.3) in patients with normal SMI and 82.6% (95% CI, 61.8–93.3) in patients with low SMI (P = 0.022). CI: confidence interval; IMAC: intramuscular adipose tissue content; OS: overall survival; SMI: skeletal muscle mass index

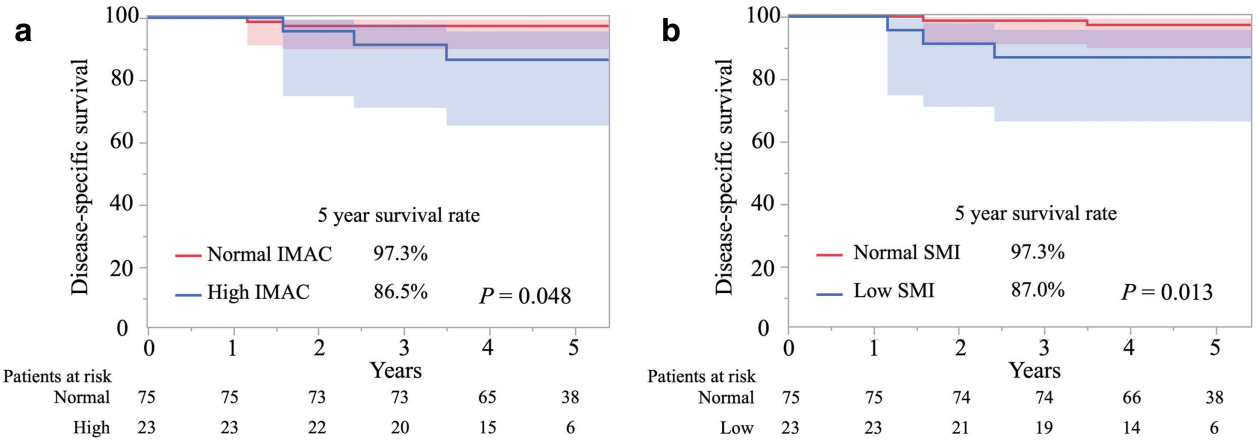

Fig. 3 DSS curves of patients classified according to the IMAC or SMI criteria. (**a**) In all cohorts, 5-year DSS was 97.3% (95% CI, 90.0–99.3) in patients with normal IMAC and 86.5% (95% CI, 65.4–95.6) in patients with high IMAC ($P = 0.048$). (**b**) In all cohorts, 5-year DSS was 97.3% (95% CI, 90.0–99.3) in patients with normal SMI and 87.0% (95% CI, 66.5–95.7) in patients with low SMI ($P = 0.013$). CI: confidence interval; DSS: disease-specific survival; IMAC: intramuscular adipose tissue content; SMI: skeletal muscle mass index

Discussion

This study compared the survival between patients stratified by gender-specific quartiles of IMAC. Patients with high IMAC had a significantly worse OS rate than those with normal IMAC, indicating that skeletal muscle quality is an important prognostic factor in patients undergoing surgery for early-stage NSCLC.

Previously, several studies have focused on the impact of BMI on postoperative outcomes in patients with lung cancer.[14] However, the results varied with each study, and the importance of BMI as a prognostic factor was controversial because it does not accurately reflect the differences in individual body composition due to the difficulty in distinguishing between muscle and fat. In recent years, it has become possible to accurately evaluate body composition in terms of muscle and fat using CT. Preoperative low skeletal muscle mass assessed by SMI, a component of sarcopenia, is a prognostic factor after surgery for various kinds of cancer, including NSCLC.[5,6,15]

Muscle strength depends not only on muscle mass but also on the accumulation of intramuscular adipose tissue. Because adipose tissue infiltration in skeletal muscles could cause cytokine level imbalance, leading to systematic dysfunction, such as insulin resistance, inflammation associated with increased inflammatory cytokines, and immune system dysfunction,[16–18] skeletal muscle quality assessed by IMAC has attracted attention as a new indicator of sarcopenia.[7–9] Recently, several studies have measured IMAC on preoperative CT and reported the impact of IMAC on survival in several diseases.[7–9,19,20] Therefore, we investigated the impact of IMAC on postoperative prognosis in patients with NSCLC. We identified the clinical impact of IMAC in patients undergoing surgery for early-stage NSCLC, especially on OS rather than DSS. Previous studies on liver cancer and lung transplantation have discussed the relationship between cytokine level imbalance and increased risk of death in patients with high IMAC.[7,15,21] However, the mechanism of how high IMAC influences prognosis has not yet been elucidated in patients with lung cancer, and further investigations are required. Additionally, previous studies showed that a high IMAC was associated with more postoperative complications.[7,9] We could not investigate the impact of IMAC on postoperative complications in this study as only a few events were observed. Further studies are warranted to investigate the impact of preoperative muscle quality on postoperative complications.

Although SMI is a well-known indicator of sarcopenia, it could be calculated as normal in patients with a large amount of intramuscular adipose tissue; measuring only muscle quantity could not identify such patients as having sarcopenia.[21] A previous study suggested that CT-determined muscle quality is a better surrogate marker of sarcopenia than muscle quantity.[22] Likewise, bivariate analysis for OS in this study showed a higher HR for survival risk in IMAC than that in SMI. Thus, measuring muscle quality as well as quantity appears to

Table 2 Bivariate analysis for the prognostic significance of IMAC

Variables	OS		DSS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
IMAC (high vs. normal)	13.7 (2.64–71.6)	0.002	4.92 (0.82–29.7)	0.082
Age (≥65 vs. <65 years)	0.91 (0.18–4.44)	0.90	1.40 (0.16–12.1)	0.76
IMAC (high vs. normal)	13.9 (2.65–73.2)	0.002	5.04 (0.84–30.2)	0.077
Sex (male vs. female)	1.11 (0.29–4.50)	0.74	0.91 (18.2–4.52)	0.91
IMAC (high vs. normal)	21.0 (3.42–128.5)	0.001	7.54 (1.12–50.6)	0.038
BMI (<18.5 vs. ≥18.5)	5.96 (0.98–36.2)	0.052	7.18 (1.16–46.2)	0.038
IMAC (high vs. normal)	12.4 (2.42–64.0)	0.003	4.98 (0.83–29.9)	0.079
Smoking (yes vs. no)	2.25 (0.45–11.3)	0.32	1.60 (0.29–8.82)	0.59
IMAC (high vs. normal)	13.7 (2.54–73.9)	0.002	4.42 (0.73–26.6)	0.11
Alb (≤4 vs. >4)	2.41 (0.64–9.12)	0.19	3.63 (0.66–20.0)	0.14
IMAC (high vs. normal)	17.2 (3.03–97.1)	0.001	6.39 (1.03–39.5)	0.046
NLR (≥3 vs. <3)	2.43 (0.55–10.6)	0.24	3.81 (0.73–20.0)	0.11
IMAC (high vs. normal)	13.6 (2.51–73.4)	0.003	4.31 (0.71–26.1)	0.11
PNI (≤40 vs. >40)	2.43 (0.64–9.18)	0.19	3.71 (0.67–20.5)	0.13
IMAC (high vs. normal)	31.8 (4.55–222.4)	<0.001	11.3 (1.53–83.6)	0.018
mGPS (1, 2 vs. 0)	12.9 (2.28–73.2)	0.004	16.3 (2.56–103.6)	0.003
IMAC (high vs. normal)	13.6 (2.63–70.6)	0.002	5.00 (0.83–30.0)	0.078
CEA (>5 vs. ≤5)	1.08 (0.13–8.89)	0.94	1.47 (0.17–12.7)	0.73
IMAC (high vs. normal)	17.6 (3.07–100.8)	0.001	5.48 (0.91–33.0)	0.063
Location (left vs. right)	2.87 (0.70–11.6)	0.14	3.32 (0.60–18.3)	0.16
IMAC (high vs. normal)	13.4 (2.60–69.3)	0.002	5.00 (0.83–30.0)	0.078
Surgery (segmentectomy vs. lobectomy)	0.82 (0.17–4.03)	0.81	0.81 (0.15–4.41)	0.80
IMAC (high vs. normal)	13.1 (2.44–70.6)	0.003	5.17 (0.86–31.2)	0.073
Histological type (AD vs. non-AD)	0.86 (0.19–3.93)	0.85	1.35 (0.15–11.8)	0.79
IMAC (high vs. normal)	17.6 (3.07–100.7)	0.001	5.63 (0.94–33.9)	0.059
LVI (positive vs. negative)	2.99 (0.74–12.1)	0.13	8.49 (0.99–73.0)	0.052
IMAC (high vs. normal)	15.6 (2.85–85.4)	0.002	4.65 (0.77–28.0)	0.093
Pleural invasion (positive vs. negative)	7.26 (1.81–29.1)	0.005	13.6 (2.44–75.6)	0.003
IMAC (high vs. normal)	11.2 (2.16–57.7)	0.004	4.28 (0.70–26.0)	0.11
Pathological stage (II vs. I)	2.55 (0.64–10.1)	0.18	4.26 (0.85–21.4)	0.079
IMAC (high vs. normal)	20.4 (3.42–121.5)	<0.001	5.77 (0.95–35.0)	0.057
SMI (low vs. normal)	6.38 (1.56–26.2)	0.010	7.21 (1.30–40.0)	0.024

AD: adenocarcinoma; Alb: albumin; BMI: body mass index; CEA: carcinoembryonic antigen; CI: confidence interval; DSS: disease-specific survival; HR: hazard ratio; IMAC: intramuscular adipose tissue content; LVI: lymphovascular invasion; mGPS: modified Glasgow prognostic score; NLR: neutrophil-to-lymphocyte ratio; OS: overall survival; PNI: prognostic nutritional index; SMI: skeletal muscle mass index

be important to predict postoperative survival risk for early-stage NSCLC.

There is no standardized measurement of skeletal muscle; therefore, identifying which slice level should be assessed on chest CT is controversial.[6] Some studies reported that the muscle mass at the L3 level was useful for predicting prognosis.[6] However, only a higher lumbar spine level can be assessed on chest CT. Further, some other studies have reported a correlation between the skeletal muscle mass at the L1 level and prognosis in patients with lung cancer.[5] In a similar manner, we assessed body compositions at the first lumbar level and our results indicated that an assessment of skeletal muscle at this level using chest CT is a valuable method. As the exact muscle to be evaluated is not established, we measured the paravertebral muscles that are generally chosen to assess sarcopenia in patients with lung cancer. Regarding the measurement of subcutaneous fat, previous studies on abdominal cancer measured subcutaneous fat in dorsal areas, whereas we measured subcutaneous fat in ventral areas; this was because accurate measurement of dorsal subcutaneous fat is often difficult on chest CTs. Further studies are needed to establish more accurate and standardized muscle quality measurements.

Although our study showed that high IMAC, i.e., low skeletal muscle quality, adversely affects postoperative prognosis, it is unclear whether preoperative interventions can lower IMAC and whether lowering

IMAC can improve prognosis for such patients with sarcopenia. Sarcopenia is associated with a lack of exercise or malnutrition. Previous studies reported that perioperative nutritional therapy, including an immunomodulating diet enriched with hydrolyzed whey peptide, branched-chain amino acid nutrients, and synbiotics, significantly improved mortality after liver transplantation.[23] In patients undergoing surgery for lung cancer, especially with poor preoperative conditions, preoperative intentional rehabilitation, including nutritional support, is beneficial and an effective approach for short-term postoperative outcomes.[24–26] In general, most patients with cancer do not have sufficient time between disease detection and the start of therapeutic interventions, such as surgery, due to rapid disease progression; therefore, preoperative nutritional interventions and rehabilitation should be performed at a reasonable time to prevent delays in surgery. Further prospective investigations are needed to determine whether preoperative short-term nutritional interventions and rehabilitation could lower IMAC and lead to better outcomes after surgery.

This study has several limitations. First, it was a single-center retrospective analysis; therefore, the sample size was relatively limited. Because of the possibility of overfitting in multivariate analysis for three or more variables due to a few events, we conducted a bivariate analysis to determine the prognostic significance of IMAC with reference to previous reports.[27,28] Second, this study lacks information about other indicators that define sarcopenia, such as grip strength or lean body mass. Third, the cutoff values of IMAC were determined using gender-specific quartiles and validation studies were not performed. These values could differ between study populations, and therefore, optimal cutoff values should be established that can be universally applied to other research in future studies.

Conclusion

This study demonstrated that preoperative skeletal muscle quality as well as quantity is an independent postoperative prognostic factor in patients with early-stage NSCLC. Furthermore, preoperative skeletal muscle quality evaluated by IMAC could be a more beneficial and promising marker for the prediction of survival risk than muscle quantity. The results of this study suggested that effective preoperative treatment strategies for patients with sarcopenia scheduled to undergo surgery need to be established for improving postoperative outcomes for early-stage NSCLC.

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Disclosure Statement

The authors have no conflicts of interest to declare.

References

1) Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015; **65**: 87–108.
2) Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; **28**(**suppl_4**): iv1–21.
3) Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the european working group on sarcopenia in older people. Age Ageing 2010; **39**: 412–23.
4) Rosenberg IH. Sarcopenia: Origins and clinical relevance. J Nutr 1997; **127**(**Suppl**): 990S–1S.
5) Sun C, Anraku M, Karasaki T, et al. Low truncal muscle area on chest computed tomography: a poor prognostic factor for the cure of early-stage non-small-cell lung cancer. Eur J Cardiothorac Surg 2019; **55**: 414–20.
6) Nishimura JM, Ansari AZ, D'Souza DM, et al. Computed tomography-assessed skeletal muscle mass as a predictor of outcomes in lung cancer surgery. Ann Thorac Surg 2019; **108**: 1555–64.
7) Hamaguchi Y, Kaido T, Okumura S, et al. Preoperative intramuscular adipose tissue content is a novel prognostic predictor after hepatectomy for hepatocellular carcinoma. J Hepatobiliary Pancreat Sci 2015; **22**: 475–85.
8) Ojima Y, Harano M, Sumitani D, et al. Impact of preoperative skeletal muscle mass and quality on the survival of elderly patients after curative resection of colorectal cancer. J Anus Rectum Colon 2019; **3**: 143–51.
9) Kiriya Y, Toshiaki N, Shibasaki I, et al. Sarcopenia assessed by the quantity and quality of skeletal muscle is a prognostic factor for patients undergoing cardiac surgery. Surg Today 2020; **50**: 895–904.
10) Goldstraw P, Crowley J, Chansky K, et al. The IASLC lung cancer staging project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2007; **2**: 706–14.

11) Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 2015; **10**: 1243–60.
12) Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nippon Geka Gakkai Zasshi 1984; **85**: 1001–5. (in Japanese)
13) Proctor MJ, Morrison DS, Talwar D, et al. An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a Glasgow Inflammation Outcome Study. Br J Cancer 2011; **104**: 726–34.
14) Wang J, Xu H, Zhou S, et al. Body mass index and mortality in lung cancer patients: a systematic review and meta-analysis. Eur J Clin Nutr 2018; **72**: 4–17.
15) Hamaguchi Y, Kaido T, Okumura S, et al. Preoperative visceral adiposity and muscularity predict poor outcomes after hepatectomy for hepatocellular carcinoma. Liver Cancer 2019; **8**: 92–109.
16) Zoico E, Rossi A, Di Francesco V, et al. Adipose tissue infiltration in skeletal muscle of healthy elderly men: relationships with body composition, insulin resistance, and inflammation at the systemic and tissue level. J Gerontol A Biol Sci Med Sci 2010; **65**: 295–9.
17) Marcus RL, Addison O, Kidde JP, et al. Skeletal muscle fat infiltration: impact of age, inactivity, and exercise. J Nutr Health Aging 2010; **14**: 362–6.
18) Delmonico MJ, Harris TB, Visser M, et al. Longitudinal study of muscle strength, quality, and adipose tissue infiltration. Am J Clin Nutr 2009; **90**: 1579–85.
19) Kitajima Y, Eguchi Y, Ishibashi E, et al. Age-related fat deposition in multifidus muscle could be a marker for nonalcoholic fatty liver disease. J Gastroenterol 2010; **45**: 218–24.
20) Kitajima Y, Hyogo H, Sumida Y, et al. Severity of non-alcoholic steatohepatitis is associated with substitution of adipose tissue in skeletal muscle. J Gastroenterol Hepatol 2013; **28**: 1507–14.
21) Hamaguchi Y, Kaido T, Okumura S, et al. Impact of quality as well as quantity of skeletal muscle on outcomes after liver transplantation. Liver Transpl 2014; **20**: 1413–9.
22) Tzeng YH, Wei J, Tsao TP, et al. Computed tomography-determined muscle quality rather than muscle quantity is a better determinant of prolonged hospital length of stay in patients undergoing transcatheter aortic valve implantation. Acad Radiol 2020; **27**: 381–8.
23) Kaido T, Ogawa K, Fujimoto Y, et al. Impact of sarcopenia on survival in patients undergoing living donor liver transplantation. Am J Transplant 2013; **13**: 1549–56.
24) Harada H, Yamashita Y, Misumi K, et al. Multidisciplinary team-based approach for comprehensive preoperative pulmonary rehabilitation including intensive nutritional support for lung cancer patients. PLoS One 2013; **8**: e59566.
25) Harada H, Takahama M, Nakao J, et al. Comprehensive preoperative pulmonary rehabilitation including intensive nutritional support reduces the postoperative morbidity rate of sarcopenia-related patients with lung cancer. Phys Med Rehabilit 2018; **2**: 1.
26) Benzo R, Wigle D, Novotny P, et al. Preoperative pulmonary rehabilitation before lung cancer resection: Results from two randomized studies. Lung Cancer 2011; **74**: 441–5.
27) Nomura K, Aokage K, Nakai T, et al. Prognostic impact of extranodal extension in patients with pN1-N2 lung adenocarcinoma. J Cancer Res Clin Oncol 2021; **147**: 3699–707.
28) Yamamoto Y, Takemoto N, Michiba T, et al. Radiotherapy alone as a possible de-intensified treatment for human papillomavirus-related locally advanced oropharyngeal squamous cell carcinoma. Int J Clin Oncol 2019; **24**: 640–8.