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**TITLE PAGE**

**Title: Preoperative Low Muscle Mass Is Associated With Major Complications and Lower Recurrence-Free Survival After Gastric Cancer Surgery**

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## **ABSTRACT**

**Background:** Low muscle mass (LMM) has been associated with postoperative morbidity.

This study aimed to examine the relationship between preoperative LMM and major postoperative complications and survival in patients undergoing curative resection for gastric cancer.

**Method:** A single-centre retrospective cohort study was conducted on consecutive patients who underwent surgical resection for gastric adenocarcinoma between 2008 and 2018. Patient demographics, radiological parameters, pathological data and complications were recorded. Skeletal muscle index was calculated using OsiriX software by manually measuring the cross-sectional skeletal muscle area at the third lumbar vertebra and correcting to the patient's height. Univariate and multivariate analyses were used to identify the risk factors associated with the outcomes.

**Results:** A total of 62 patients (36 males, mean age  $68.3 \pm 1.5$  years) met the inclusion criteria. Twenty-six patients (41.9%) had LMM preoperatively. Demographic data in the non-LMM and LMM groups were equally matched except for body mass index ( $27.6 \pm 0.8$  kg/m<sup>2</sup> vs  $24.3 \pm 1.1$  kg/m<sup>2</sup>;  $p=0.012$ ) and serum albumin ( $36.7 \pm 0.7$  g/l vs  $33.8 \pm 1.0$  g/l;  $p=0.017$ ), which were higher in the non-LMM. LMM was associated with higher incidence of total (35.5% vs 64.5%;  $p=0.006$ ), minor (40% vs 60%;  $p=0.030$ ), major (9.1% vs 90.9%;  $p=0.004$ ) postoperative complications, and decreased recurrence-free survival (hazard ratio 2.29; 95% CI 1.10 – 4.77;  $p=0.027$ ).

**Conclusion:** LMM is a significant independent risk factor for major postoperative complications and recurrence-free survival after gastrectomy. Preoperative identification of

LMM could be a useful tool for prognostication and may identify a group suitable for prehabilitation.

**Keywords:** Low muscle mass, Gastrectomy, Skeletal muscle index

## **INTRODUCTION**

Gastric cancer is the fifth most common malignancy and the third most common cause of cancer-related death worldwide.<sup>1</sup> Multi-modality therapy for gastric cancer provides the highest chance for a cure; however, surgical resection is the mainstay of treatment.<sup>2</sup> Enhancement in surgical techniques and perioperative care for gastric cancer has decreased overall postoperative morbidity and mortality, yet the incidence of these remain high.<sup>3</sup>

Sarcopenia is defined by the European Working Group on Sarcopenia in Older People (EWGSOP) as a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength correlated with physical disability, poor quality of life and death.<sup>4</sup> The rationale for the use of both muscle mass and strength is that muscle strength does not depend solely on mass, and the relationship between strength and mass is not linear.<sup>4</sup>

EWGSOP recommended using skeletal muscle index measurement to identify low muscle mass (LMM).<sup>4</sup> There are multiple tools for measuring skeletal muscle index (SMI), including bioelectrical impedance analysis, dual-energy X-ray absorptiometry, magnetic resonance imaging, and computed tomography (CT) scan.<sup>4,5</sup> With significant advances in its technology, CT has become the most commonly used cross-sectional imaging modality and the standard imaging tool in daily clinical settings.

There is a well-established negative relationship between sarcopenia or LMM and surgical patient outcomes that have been investigated in a number of different cancers such as oesophageal,<sup>6</sup> pancreatic,<sup>7</sup> colorectal,<sup>8</sup> and liver<sup>9</sup> malignancies. However, there is a relative paucity of published data examining this relationship for gastric cancer.<sup>10</sup> The calculation of SMI on computed tomography (CT) scan prior to surgery and identification of patients with LMM may be useful to help prognostication and also to help stratify higher-risk individuals.

This study aimed to determine the association of preoperative LMM defined by SMI on postoperative hospital and intensive care unit (ICU) length of stay (LOS), morbidity, long-term overall survival (OS) and recurrence-free survival (RFS) in patients who underwent potentially curative resection for gastric cancer.

## **MATERIALS AND METHODS**

All patients with gastric adenocarcinoma who underwent curative-intent gastrectomy between 1<sup>st</sup> January 2008 and 31<sup>st</sup> December 2018 were retrospectively identified through a review of procedure codes from the International Classification of Diseases Tenth Revision, Clinical Modifications (ICD-10-CM) and cross-referenced with postoperative histopathological data.

Patients who had a staging CT scan within three months of surgery were included. If a patient had multiple CT scans within three months of surgery, the initial staging CT was utilised for SMI assessment. Patient information was obtained by review of both paper and electronic medical records including demographics, neoadjuvant therapy type (i.e.: Epirubicin, Cisplatin, and 5-fluorouracil [ECF]; Docetaxel, Oxaliplatin, Leucovorin, and 5-fluorouracil [FLOT]; Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma [TOP GEAR]), comorbidities, surgical parameters (i.e. type and methods of surgery), postoperative tumour staging according to the American Joint Committee on Cancer (AJCC) eighth edition,<sup>11</sup> and postoperative complications, ICU- and hospital LOS. The Charlson Comorbidity Index (CCI) was calculated from patient preoperative information. The severity of complications was graded according to the Clavien-Dindo classification system, with minor complications defined as Clavien-Dindo < 3a and major

complications as Clavien-Dindo  $\geq 3a$ .<sup>12, 13</sup> All patients underwent dietitian review for nutritional assessment at baseline with follow up depending on their level of nutritional risk.

### *Diagnosis of LMM*

The diagnosis of LMM was made based on the staging CT scan, which was performed prior to neoadjuvant therapy (if patients underwent neoadjuvant) or preoperatively (if no neoadjuvant treatment was used), and was consistent for all patients. CT scans were analysed using the OsiriX software version 5.0.2 32-bit. CT images were analysed by a reviewer blinded to the patients' demographics and outcome using the following standardised approach. Two sequential scans at the third lumbar vertebra, in which both transverse processes were visible, were selected. Skeletal muscle coverage was defined using -30 to +150 Hounsfield unit thresholds.<sup>14</sup> The average hand-drawn muscle area of these two images was used. SMI was defined as the cross-sectional skeletal muscle area ( $\text{cm}^2$ ) normalised with the patient's height (m). Subsequently, all images and measurements were verified by a Board-Certified Radiologist. LMM thresholds defined by Martin et al.<sup>5</sup> are commonly cited and used for patient stratifications; these are derived from a cohort of lung or gastrointestinal cancer patients and the threshold was adjusted for men according to their BMI. LMM in women is defined as an SMI being below  $41 \text{ cm}^2/\text{m}^2$ . In men with  $\text{BMI} < 25 \text{ kg}/\text{m}^2$ , LMM is defined as an SMI below  $43 \text{ cm}^2/\text{m}^2$  and in men with  $\text{BMI} \geq 25 \text{ kg}/\text{m}^2$  LMM is defined as an SMI below  $53 \text{ cm}^2/\text{m}^2$ .<sup>5</sup> An example of an analysed CT scan between non-LMM and LMM patients is shown in Figure 1.

### *Statistical analysis*

Statistical analysis was performed using the IBM SPSS v26.0 software (IBM, NY, USA).

The independent t-test and Mann-Whitney U test were used to compare continuous variables.

The  $\chi^2$  test and Fisher's exact test were used to compare categorical variables. Cox proportional hazard modelling was used to determine independent predictors of survival. Generalised linear model was used to determine univariate and multivariate predictors for morbidity. Univariable predictors yielding  $p < 0.2$  were entered into the multivariable model as covariates. The association between LMM and outcomes of interest was analysed by univariate and multivariate regression analyses. All data were expressed as mean  $\pm$  standard error of mean (SEM) and statistical significance was defined as a p-value  $< 0.05$ .

## **RESULTS**

Ninety-three patients underwent curative-intent gastrectomy for gastric cancer during the study period. Twenty patients were excluded as they did not have available CT scans within the required time frame. Eleven patients were treated for disease other than adenocarcinoma and therefore excluded. The remaining 62 patients (36 males and 26 females; mean age  $68.3 \pm 1.5$  years) were included in the study. Patient demographics, clinical indices and pathological data are summarised in Table 1. The non-LMM and LMM groups were well matched based on preoperative characteristics, including comorbidities, except for BMI and serum albumin, which were significantly lower in the LMM group.

There was a mean of 28 days from the date of the preoperative CT scan to the date of surgery. The distribution of SMI values is shown in Figure S1. The overall mean SMI was  $46.1 \text{ cm}^2/\text{m}^2$  (Figure S1A) with the average values for men and women  $48.9 \text{ cm}^2/\text{m}^2$  (Figure S1B) and  $42.2 \text{ cm}^2/\text{m}^2$  (Figure S1C), respectively. According to the definition by Martin et al. of SMI threshold values,<sup>5</sup> 26 patients (41.9%; 15 males and 11 females) demonstrated preoperative LMM.

Operative details and postoperative outcomes are shown in Table S1 and Table S2, respectively. There was no statistically significant difference in the pathological staging, total LOS and the number of ICU bed hours between the two groups ( $p=0.35$ ,  $p=0.06$  and  $p=0.24$ , respectively). The mean follow-up time was 29.6 months. A summary of univariate and multivariate cox regression analyses for OS and RFS is presented in Table 2A and Table 2B, respectively. In the univariate regression analysis, LMM and tumour stages  $\geq 3A$  were statistically significant prognosticators of both OS and RFS. In the multivariate analysis, only tumour stages  $\geq 3A$  (HR 4.16; 95%CI: 1.14 - 15.15;  $p=0.030$ ) was a significant predictor of poor OS and only LMM (HR 2.29; 95%CI: 1.10 - 4.77;  $p=0.027$ ) was a significant predictor of poor RFS.

One or more postoperative complications occurred in 35 (56.5%) patients, which was higher in the LMM group (20 [76.9%] patients vs. 15 [41.7%] patients;  $p=0.017$ ). The LMM group had significantly higher rates of total complications (49 [64.5%] vs 27 [35.5%] complications;  $p=0.006$ ), minor complications (39 [60%] vs 26 [40%] complications;  $p=0.030$ ), and major complications (10 [90.9%] vs 1 [9.1%] complications;  $p=0.004$ ) as illustrated in Figure 2A. Preoperative LMM was also specifically associated with a higher incidence of complications in pulmonary and gastrointestinal systems ( $p=0.003$  and  $p=0.003$ , respectively), Figure 2B. The incidence of pulmonary and gastrointestinal complications is shown in Table S3. Univariate and multivariate regression analyses that were used to identify factors associated with major complications are shown in Table 3. LMM was a significant predictor in univariate and multivariate analysis for incidence of major complications.

## **DISCUSSION**

This study provides further evidence in support of the adverse relationship between preoperative LMM and postoperative outcomes following curative-intent gastrectomy. Previous studies have investigated this relationship.<sup>15-17</sup> Consistent with this study, LMM has been associated with lower serum albumin,<sup>16, 18</sup> an increase in the incidence of major postoperative complications,<sup>15, 18, 19</sup> decreased RFS,<sup>16, 20</sup> but no increase in postoperative ICU stay or hospital LOS,<sup>19, 21</sup> and OS.<sup>17</sup>

In this series LMM was a significant predictor of OS in the univariate analysis, however was not a statistically significant predictor in the multivariate analysis of OS. This outcome may have been confounded due to the small sample size and loss to follow up; however, is consistent with previous published studies.<sup>22-24</sup>

LMM in cancer patients is partly due to cachexia-associated processes.<sup>25</sup> The number of studies in cancer patients investigating the association between LMM and clinical outcomes is rapidly increasing.<sup>7, 10</sup> However, as yet, there is no consensus on a standard approach to measure LMM, and different cut-off points or devices, have been published.<sup>4</sup>

Sarcopenia is characterised as a progressive loss of skeletal muscle mass and strength, associated with poor quality of life.<sup>4</sup> Sarcopenia is dependent on the relationship between LMM, low muscle strength, and impaired physical performance.<sup>4</sup> Rather than being a direct surrogate of sarcopenia, LMM is one of the key factors involved in its development and has previously been associated with an increased incidence of postoperative complications.<sup>26</sup>

Future research endeavours that encompass the functional deficits of sarcopenia, as opposed to a purely radiological diagnosis, would be of great value in understanding the clinical outcomes of this disease process.

The specific mechanisms which underly the relationship between LMM and poor outcomes in patients with gastric cancer remain poorly defined. Skeletal muscle has been identified as a potential central regulator of the immune system.<sup>25</sup> In LMM patients, this interaction may be disturbed, leading to chronic, low-grade inflammation resulting in immune dysfunction.<sup>27, 28</sup> These factors may, in part, explain the relationship between LMM and the higher risk of complications.<sup>28, 29</sup>

Pulmonary complications are more frequent in the LMM group. Previous publications have documented in LMM a decline in the ability to perform activities of daily living, delayed mobilisation,<sup>19</sup> and impairment of respiratory<sup>30</sup> and swallowing muscle groups (leading to difficulty clearing the airway after surgery).<sup>31</sup> All of these factors, especially in patients with preoperative lung disease, may result in a higher incidence of postoperative pneumonia and atelectasis. In addition, LMM-related impaired immune response and increased inflammatory activity may contribute to the development of pneumonia.<sup>32, 33</sup>

In various malignancy types, tumour stage has previously been shown to be related to LMM and worse outcome.<sup>34, 35</sup> In patients with advanced gastric cancer, this may be magnified by additional insufficient oral intake, secondary to disease-specific symptoms, such as dysphagia, nausea, vomiting, loss of appetite and effects of mechanical obstruction can be associated with concurrent nutritional depletion and result in a worsening muscle loss and postoperative complications.<sup>19</sup>

Increased awareness among patients and healthcare providers, early screening, and a multi-disciplinary approach, especially personalised dietitian input to the treatment of LMM before surgical intervention, may be the best current practice to minimise the overall adverse impact

of LMM and subsequently postoperative complications in this group.<sup>36,37</sup> It is recommended that surgical units ensure patients are routinely reviewed by a dietitian after cancer diagnosis and perioperatively. In 2010, the Society for Sarcopenia, Cachexia and Wasting Disease purported that adequate energy and protein intake in addition to the importance of physical exercise have been emphasised as the pivotal components in the management of sarcopenia and muscle loss.<sup>38</sup> A minimum of 20 to 30 minutes of resistance and aerobic exercise three times a week is recommended to slow muscle loss and sarcopenia.<sup>38</sup> It is extremely important to note that adequate protein supplementation alone only slows, but does not stop, loss of muscle mass, or results in muscle gain.<sup>38</sup>

Improvement of postoperative outcomes has been demonstrated in sarcopenic gastric cancer patients with preoperative exercise and nutritional support.<sup>39</sup> Following an assessment of calorie and protein intake in preoperative sarcopenic patients, nutritional support was provided for three weeks aiming for sufficient daily intake of calories and protein, in addition to preoperative exercise interventions which consisted of handgrip training, walking and resistance training.<sup>39</sup> In this series by Yamamoto et al, no major complications were seen in the sarcopenic group, suggesting that even with a very short period of intervention, preoperative nutritional and exercise interventions can be beneficial.<sup>39</sup>

Several limitations can be noted within our study. Firstly, observational bias is a potential drawback of any retrospective study as this may have influenced the data collection process through under-reporting both variables and outcome. The study was completed at a single centre and may have therefore suffered from selection bias and limits the ability to generalise our results to other centres. Even though the results are comparable with similar papers studying the effect of LMM in different types of cancer patients, the number of patients was

relatively small. On the other hand, this study confirmed the findings in previous studies which demonstrated a robust association between LMM and negative outcomes. Fourthly, we recognised that diverse ethnicities have different normal skeletal muscle mass cut-offs; however, the ethnicity of patients was not recorded as part of our database. Additional research is required to determine the difference of LMM's cut-off values between ethnicities. Furthermore, the definition of LMM group was based on patients with gastric cancer, which was appropriate in this setting. However, we acknowledged that this group might deviate from the standard definitions of LMM in healthy adults. The confounding variables, such as operation type and stage, might closely correlate with LMM, which was uncontrolled in this retrospective study. Future prospective research is suggested to define the effects of these variables.

## **CONCLUSION**

LMM is significantly associated with increased major postoperative complications and poorer recurrence-free survival in patients undergoing gastrectomy for gastric cancer.

Preoperative identification and management of LMM may help identify higher-risk patients and improve clinical outcomes after gastrectomy.

## **REFERENCES**

- [1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018; 68:394-424.
- [2] Ajani JA, D'Amico TA, Almhanna K, et al. Gastric Cancer, Version 3.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2016; 14:1286-312.
- [3] Zhou J, Zhou Y, Cao S, et al. Multivariate logistic regression analysis of postoperative complications and risk model establishment of gastrectomy for gastric cancer: A single-center cohort report. *Scand J Gastroenterol.* 2016; 51:8-15.
- [4] 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.
- [5] 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; 31:1539-47.
- [6] Boshier PR, Heneghan R, Markar SR, Baracos VE, Low DE. Assessment of body composition and sarcopenia in patients with esophageal cancer: a systematic review and meta-analysis. *Dis Esophagus.* 2018; 31.
- [7] Mintziras I, Miligkos M, Wachter S, Manoharan J, Maurer E, Bartsch DK. Sarcopenia and sarcopenic obesity are significantly associated with poorer overall survival in patients with pancreatic cancer: Systematic review and meta-analysis. *Int J Surg.* 2018; 59:19-26.
- [8] Kroenke CH, Prado CM, Meyerhardt JA, et al. Muscle radiodensity and mortality in patients with colorectal cancer. *Cancer.* 2018; 124:3008-15.
- [9] Hiraoka A, Otsuka Y, Kawasaki H, et al. Impact of muscle volume and muscle function decline in patients undergoing surgical resection for hepatocellular carcinoma. *J Gastroenterol Hepatol.* 2018; 33:1271-6.
- [10] Shen Y, Hao Q, Zhou J, Dong B. The impact of frailty and sarcopenia on postoperative outcomes in older patients undergoing gastrectomy surgery: a systematic review and meta-analysis. *BMC Geriatr.* 2017; 17:188.
- [11] Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin.* 2017; 67:93-9.
- [12] Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg.* 2009; 250:187-96.
- [13] 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; 240:205-13.
- [14] Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol (1985).* 1998; 85:115-22.
- [15] O'Brien S, Twomey M, Moloney F, et al. Sarcopenia and Post-Operative Morbidity and Mortality in Patients with Gastric Cancer. *J Gastric Cancer.* 2018; 18:242-52.
- [16] Zhuang CL, Huang DD, Pang WY, et al. Sarcopenia is an Independent Predictor of Severe Postoperative Complications and Long-Term Survival After Radical Gastrectomy for Gastric Cancer: Analysis from a Large-Scale Cohort. *Medicine (Baltimore).* 2016; 95:e3164.
- [17] Tegels JJ, van Vugt JL, Reisinger KW, et al. Sarcopenia is highly prevalent in patients undergoing surgery for gastric cancer but not associated with worse outcomes. *J Surg Oncol.* 2015; 112:403-7.

- [18] Zhang WT, Lin J, Chen WS, et al. Sarcopenic Obesity Is Associated with Severe Postoperative Complications in Gastric Cancer Patients Undergoing Gastrectomy: a Prospective Study. *J Gastrointest Surg.* 2018; 22:1861-9.
- [19] 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; 19:986-93.
- [20] Sato T, Aoyama T, Maezawa Y, et al. Impact of preoperative sarcopenia on recurrence in gastric cancer surgery. American Society of Clinical Oncology, 2016.
- [21] Lou N, Chi CH, Chen XD, et al. Sarcopenia in overweight and obese patients is a predictive factor for postoperative complication in gastric cancer: A prospective study. *Eur J Surg Oncol.* 2017; 43:188-95.
- [22] Black D, Mackay C, Ramsay G, et al. Prognostic Value of Computed Tomography: Measured Parameters of Body Composition in Primary Operable Gastrointestinal Cancers. *Ann Surg Oncol.* 2017; 24:2241-51.
- [23] Choi MH, Kim KA, Hwang SS, Byun JY. CT-quantified muscle and fat change in patients after surgery or endoscopic resection for early gastric cancer and its impact on long-term outcomes. *Medicine (Baltimore).* 2018; 97:e13878.
- [24] Park HS, Kim HS, Beom SH, et al. Marked Loss of Muscle, Visceral Fat, or Subcutaneous Fat After Gastrectomy Predicts Poor Survival in Advanced Gastric Cancer: Single-Center Study from the CLASSIC Trial. *Ann Surg Oncol.* 2018; 25:3222-30.
- [25] Nelke C, Dziewas R, Minnerup J, Meuth SG, Ruck T. Skeletal muscle as potential central link between sarcopenia and immune senescence. *EBioMedicine.* 2019; 49:381-8.
- [26] Kamarajah SK, Bundred J, Tan BHL. Body composition assessment and sarcopenia in patients with gastric cancer: a systematic review and meta-analysis. *Gastric Cancer.* 2019; 22:10-22.
- [27] Bano G, Trevisan C, Carraro S, et al. Inflammation and sarcopenia: A systematic review and meta-analysis. *Maturitas.* 2017; 96:10-5.
- [28] Dalle S, Rossmeislova L, Koppo K. The Role of Inflammation in Age-Related Sarcopenia. *Front Physiol.* 2017; 8:1045.
- [29] Prado CM, Heymsfield SB. Lean tissue imaging: a new era for nutritional assessment and intervention. *JPEN J Parenter Enteral Nutr.* 2014; 38:940-53.
- [30] Bahat G, Tufan A, Ozkaya H, et al. Relation between hand grip strength, respiratory muscle strength and spirometric measures in male nursing home residents. *Aging Male.* 2014; 17:136-40.
- [31] Wakabayashi H, Sakuma K. Rehabilitation nutrition for sarcopenia with disability: a combination of both rehabilitation and nutrition care management. *J Cachexia Sarcopenia Muscle.* 2014; 5:269-77.
- [32] Lutz CT, Quinn LS. Sarcopenia, obesity, and natural killer cell immune senescence in aging: altered cytokine levels as a common mechanism. *Aging (Albany NY).* 2012; 4:535-46.
- [33] Xu J, Zheng B, Zhang S, et al. Effects of preoperative sarcopenia on postoperative complications of minimally invasive oesophagectomy for oesophageal squamous cell carcinoma. *J Thorac Dis.* 2019; 11:2535-45.
- [34] Aversa Z, Costelli P, Muscaritoli M. Cancer-induced muscle wasting: latest findings in prevention and treatment. *Therapeutic advances in medical oncology.* 2017; 9:369-82.
- [35] Roukos DH, Agnantis NJ. Gastric cancer: diagnosis, staging, prognosis. *Gastric Breast Cancer.* 2002; 11:7-10.
- [36] Calvani R, Miccheli A, Landi F, et al. Current nutritional recommendations and novel dietary strategies to manage sarcopenia. *J Frailty Aging.* 2013; 2:38-53.
- [37] Dhillon RJ, Hasni S. Pathogenesis and Management of Sarcopenia. *Clin Geriatr Med.* 2017; 33:17-26.

[38] Morley JE, Argiles JM, Evans WJ, et al. Nutritional recommendations for the management of sarcopenia. *J Am Med Dir Assoc.* 2010; 11:391-6.

[39] Yamamoto K, Nagatsuma Y, Fukuda Y, et al. Effectiveness of a preoperative exercise and nutritional support program for elderly sarcopenic patients with gastric cancer. *Gastric Cancer.* 2017; 20:913-8.

## **FIGURE LEGENDS**

Figure 1. Representative axial CT scan of non-low muscle mass patient (A) with a skeletal muscle index of 51.8 cm<sup>2</sup>/m<sup>2</sup> and low muscle mass patient (B) with a skeletal muscle index of 33.2 cm<sup>2</sup>/m<sup>2</sup>. The total skeletal muscle area (outlined in green) was measured on a CT slice at the level of third lumbar vertebra.

Figure 2. Complications between non-low muscle mass (LMM) and LMM groups. Minor and major complications (A) and complications per organ system (B).

## **LIST OF SUPPORTING INFORMATION**

1. Document S1 (Ethics and funding)
2. Table S1 (Comparison of intraoperative data between non-low muscle mass and low muscle mass groups)
3. Table S2 (Comparison of postoperative data between non-low muscle mass and low muscle mass groups)
4. Table S3 (Pulmonary and gastrointestinal complications between non-low muscle mass and low muscle mass groups)
5. Figure S1 (Skeletal muscle index distribution in all-(A), male-(B), and female (C) patients with gastric adenocarcinoma)

## TABLES

Table 1. Patient demographic and characteristics

Characteristics	All (n = 62)	Non-LMM (n = 36)	LMM (n = 26)	p-value
Age (years)	68.3 ± 1.5	67.3 ± 12.0	69.8 ± 2.1	0.40
Sex (%)				0.96
Male	36 (58.1)	21 (58.3)	15 (57.7)	
Female	26 (41.9)	15 (41.7)	11 (42.3)	
Height (cm)	165.9 ± 1.3	165.8 ± 2.0	165.9 ± 1.7	0.97
Weight (kg)	72.1 ± 2.0	75.6 ± 2.1	67.4 ± 3.5	0.05
<b>BMI (kg/m<sup>2</sup>)</b>	<b>26.2 ± 0.7</b>	<b>27.6 ± 0.8</b>	<b>24.3 ± 1.1</b>	<b>0.012</b>
Charlson Comorbidity Index				<b>0.65</b>
Total score 1	0 (0.0)	0 (0.0)	0 (0.0)	
Total score 2	5 (8.1)	4 (11.1)	1 (3.8)	
Total score 3	6 (9.7)	2 (5.6)	4 (15.4)	
Total score 4	12 (19.4)	8 (22.2)	4 (15.4)	
Total score 5	14 (22.6)	8 (22.2)	6 (23.1)	
Total score 6	12 (19.4)	7 (19.4)	5 (19.2)	
Total score 7	6 (9.7)	2 (5.6)	4 (15.4)	
Total score 8	5 (8.1)	4 (11.1)	1 (3.8)	
Total score 9	0 (0.0)	0 (0.0)	0 (0.0)	
Total score 10	2 (3.2)	1 (2.8)	1 (3.8)	
Neoadjuvant therapy (%)				0.73
No therapy	39 (62.9)	22 (61.1)	17 (65.4)	
Chemotherapy ECF	15 (24.2)	10 (27.8)	5 (19.2)	
Chemotherapy FLOT	5 (8.1)	3 (8.3)	2 (7.7)	
Chemotherapy TOPGEAR	3 (4.8)	1 (2.8)	2 (7.7)	
ASA score (%)				0.31
Grade I	1 (1.6)	0 (0)	1 (3.8)	
Grade II	21 (33.9)	12 (33.3)	9 (34.6)	
Grade III	37 (59.7)	21 (58.3)	16 (61.5)	
Grade IV	3 (4.8)	3 (8.3)	0 (0)	
ECOG status (%)				0.33
0	52 (83.9)	32 (88.9)	20 (76.9)	
1	6 (9.7)	3 (8.3)	3 (11.5)	
2	4 (6.5)	1 (2.8)	3 (11.5)	
3 - 5	0 (0.0)	0 (0.0)	0 (0.0)	
Smoking status (%)				0.45
Never-smoked	29 (47.5)	17 (48.6)	12 (46.2)	
Ex-smoker	22 (36.1)	14 (40.0)	8 (30.8)	
Current smoker	10 (16.4)	4 (11.4)	6 (23.1)	
Preoperative blood test				
<b>Albumin (g/L)</b>	<b>35.4 ± 0.6</b>	<b>36.7 ± 0.7</b>	<b>33.8 ± 1.0</b>	<b>0.017</b>
CRP (mg/L)	11.8 ± 2.1	9.3 ± 1.9	15.4 ± 4.2	0.16
WCC (x10 <sup>9</sup> /L)	7.7 ± 0.4	7.9 ± 0.5	7.5 ± 0.6	0.60
Neutrophil (x10 <sup>9</sup> /L)	4.9 ± 0.3	5.1 ± 0.5	4.5 ± 0.3	0.32
Lymphocyte (x10 <sup>9</sup> /L)	2.1 ± 0.2	2.1 ± 0.2	2.2 ± 0.5	0.70
Platelet (x10 <sup>9</sup> /L)	276.4 ± 11.4	266.3 ± 13.6	289.7 ± 19.5	0.31
Neutrophil-Lymphocyte ratio	3.5 ± 0.6	3.8 ± 0.9	3.1 ± 0.5	0.50

Platelet-Lymphocyte ratio	168.3 ± 11.8	157.8 ± 15.7	182.0 ± 18.0	0.31
Pathological staging				0.35
0	4 (6.5)	3 (8.3)	1 (3.8)	
1A	6 (9.7)	4 (11.1)	2 (7.7)	
1B	4 (6.5)	2 (5.6)	2 (7.7)	
2A	9 (14.5)	6 (16.7)	3 (11.5)	
2B	16 (25.8)	10 (27.8)	6 (23.1)	
3A	13 (21.0)	8 (22.2)	5 (19.2)	
3B	6 (9.7)	1 (2.8)	5 (19.2)	
3C	2 (3.2)	2 (5.6)	0 (0.0)	
4	2 (3.2)	0 (0.0)	2 (7.7)	

LMM: low muscle mass; BMI: body mass index; ECF: Epirubicin, Cisplatin, and 5-

flourouracil; FLOT: Docetaxel, Oxaliplatin, Leucovorin, and 5-fluorouracil; TOP GEAR: Trial

of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma; ASA:

American Society of Anaesthesiologists; ECOG: Eastern Cooperative Oncology Group;

CRP: C-reactive protein; WCC: white cell count

Table 2. Univariate and multivariate cox regression analyses of overall survival (A) and recurrence-free survival (B)

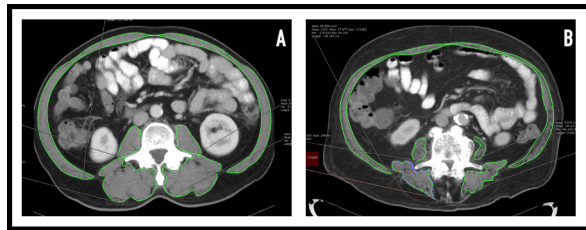
2A. Characteristics	Univariate OS			Multivariate OS		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.01	0.98 - 1.05	0.48			
Sex (male)	1.46	0.71 - 2.99	0.30			
BMI	0.97	0.90 - 1.06	0.52			
<b>Low muscle mass</b>	<b>2.17</b>	<b>1.02 - 4.63</b>	<b>0.044</b>	1.948	0.91 - 4.19	0.088
Current smoker	1.18	0.45 - 3.08	0.74			
ASA score $\geq 3$	1.16	0.53 - 2.55	0.71			
ECOG status $\geq 2$	2.14	0.64 - 7.20	0.22			
CCI $\geq 5$	0.80	0.39 - 1.65	0.54			
Neoadjuvant therapy	0.63	0.29 - 1.37	0.24			
Albumin	0.97	0.89 - 1.06	0.54			
Total gastrectomy	1.67	0.81 - 3.47	0.17	1.17	0.54 - 2.53	0.69
Stage						
$\leq 1B$	1			1		
2A – 2B	2.82	0.80 - 9.91	0.11	2.54	0.72 - 9.01	0.15
$\geq 3A$	<b>4.81</b>	<b>1.38 - 16.77</b>	<b>0.014</b>	<b>4.16</b>	<b>1.14 - 15.15</b>	<b>0.030</b>
2B. Characteristics	Univariate RFS			Multivariate RFS		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.01	0.98 - 1.04	0.52			
Sex (male)	1.65	0.83 - 3.27	0.15	1.71	0.84 - 3.49	0.14
BMI	0.95	0.88 - 1.03	0.21			
<b>Low muscle mass</b>	<b>2.56</b>	<b>1.25 - 5.26</b>	<b>0.010</b>	<b>2.29</b>	<b>1.10 - 4.77</b>	<b>0.027</b>
Current smoker	1.02	0.39 - 2.63	0.98			
ASA score $\geq 3$	1.00	0.48 - 2.06	0.99			
ECOG status $\geq 2$	2.72	0.94 - 7.85	0.06	1.41	0.49 - 4.06	0.53
CCI $\geq 5$	0.83	0.42 - 1.67	0.61			
Neoadjuvant therapy	0.77	0.37 - 1.59	0.48			
Albumin	0.97	0.90 - 1.05	0.48			
Total gastrectomy	1.66	0.83 - 3.33	0.15	1.20	0.58 - 2.49	0.63
Stage						
$\leq 1B$	1			1		
2A – 2B	1.69	0.60 - 4.75	0.32	1.34	0.47 - 3.83	0.59
$\geq 3A$	<b>3.11</b>	<b>1.13 - 8.57</b>	<b>0.028</b>	2.45	0.86 - 6.99	0.09

BMI: body mass index; ASA: American Society of Anaesthesiologists; ECOG: Eastern Cooperative Oncology Group; CCI: Charlson Comorbidity Index; OS: overall survival; RFS: recurrence-free survival

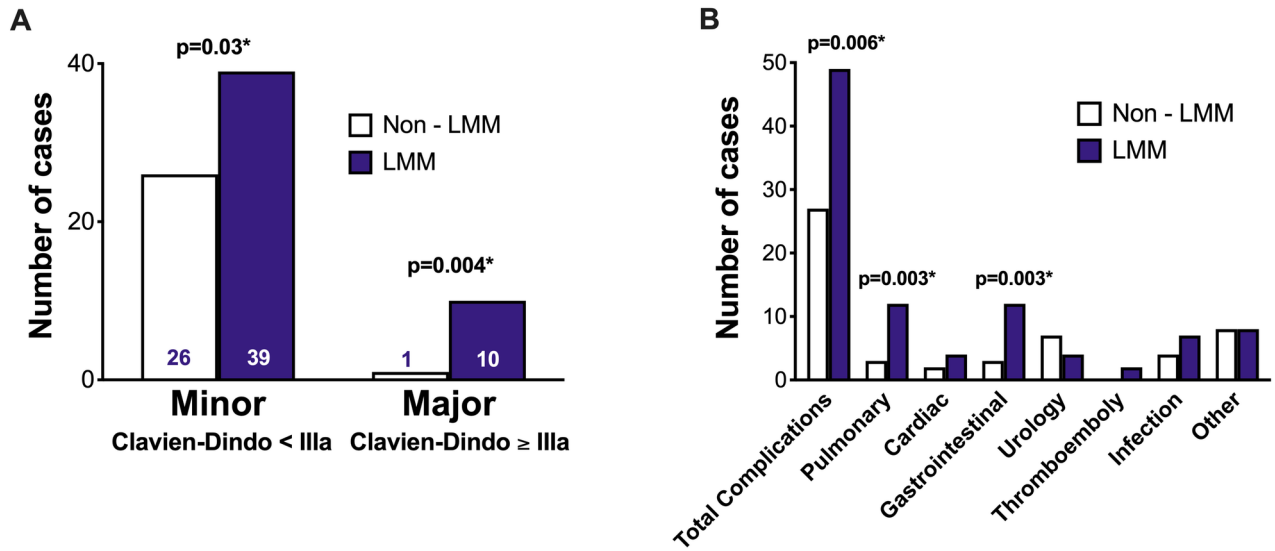
Table 3. Univariate and multivariate regression analyses for risk factors of major complications.

Characteristics	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.02	0.95 - 1.09	0.57			
Sex (male)	0.65	0.15 - 2.89	0.57			
BMI	0.93	0.80 - 1.08	0.34			
<b>Low muscle mass</b>	<b>15.56</b>	<b>1.80 - 134.24</b>	<b>0.013</b>	<b>12.87</b>	<b>1.42 - 116.50</b>	<b>0.023</b>
Current smoker	1.67	0.19 - 15.10	0.65			
ASA score $\geq 3$	1.12	0.25 - 4.99	0.88			
ECOG status $\geq 2$	2.08	0.19 - 22.58	0.55			
CCI $\geq 5$	1.21	0.27 - 5.40	0.80			
Neoadjuvant therapy	1.43	0.34 - 5.98	0.62			
Albumin	0.89	0.76 - 1.03	0.12	0.95	0.81 - 1.11	0.48
Total gastrectomy	1.22	0.29 - 5.07	0.79			
Stage						
$\leq 1B$	1					
2A – 2B	1.18	0.19 - 7.37	0.86			
$\geq 3A$	1.08	0.16 - 7.44	0.94			

BMI: body mass index; ASA: American Society of Anaesthesiologists; ECOG: Eastern Cooperative Oncology Group; CCI: Charlson Comorbidity Index



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ANS\_16590\_Figure 2.tiff