Preoperative nutritional risk index and postoperative one-year skeletal muscle loss can predict the prognosis of patients with gastric cancer: a registry based study

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Abstract

Background: Patients with gastric cancer have increased nutritional risk and experience a significant skeletal muscle loss after surgery. We aimed to determine whether muscle loss during the first postoperative year and nutritional status are indicators for predicting prognosis.

Methods: From a gastric cancer registry, a total of 958 patients who received curative gastrectomy followed by chemotherapy for stage 2 and 3 gastric cancer and survived longer than 1 year were investigated. Clinical and laboratory data were collected. Skeletal muscle index (SMI) was assessed based on the muscle area at the L3 level on abdominal computed tomography.

Results: Preoperative nutritional risk index (NRI) and postoperative decrement of SMI (dSMI) were significantly associated with overall survival (hazards ratio: 0.972 [95% CI: 0.958-0.986] and 1.058 [95% CI: 1.033-1.085], respectively) in a multivariate Cox regression analysis. Recurrence, tumor stage, comorbidity, and the preoperative muscle and subcutaneous fat area were also significant prognostic indicators. Kaplan-Meier analyses exhibited that patients with higher NRI had a significantly longer survival than those with lower NRI (3-year overall survival: 84.6% vs. 72.9%, \( P < 0.001 \)). In addition, a significantly better prognosis was observed in a patient group with less decrease of SMI (3-year overall survival: 85.6% vs. 74.5%, \( P = 0.009 \)). A logistic regression analysis demonstrated that the performance of preoperative NRI and dSMI in mortality prediction was quite significant (AUC: 0.63, \( P < 0.001 \)) and the combination of clinical factors enhanced the predictive accuracy to the AUC of 0.90 (\( P < 0.001 \)). This prognostic relevance of NRI and dSMI was maintained in patients experiencing tumor recurrence.

Conclusions: Skeletal muscle loss during the first postoperative year and preoperative NRI are predictors of overall survival in stage 2 or 3 gastric cancer patients regardless of relapse. Our results support the potential importance of exercise and nutritional support along with standard treatment.

Background

Surgery is the mainstay of curative treatment for gastric cancer. Gastrectomy induces physiologic derangements including worsened nutritional status, significant weight loss, and decreased muscle and fat volume. The loss of stomach reservoir function, rapid intestinal transit time, and foods bypassing the proximal small intestine are responsible for these postoperative changes.\(^1\)–\(^3\).

In the first year after gastrectomy, most patients experience dramatic physiologic changes, like cascade of sarcopenia and malnutrition. Indeed, our prior study demonstrated that skeletal muscle mass and nutritional parameters decrease sharply for the first three months and slowly decrease for the remaining nine months, eventually leading to a loss of 8–15% of the initial body weight and 3–5% of the muscle area.\(^3\) In addition, adjuvant chemotherapy, which is the standard treatment in stage 2 and 3 gastric cancer, exacerbates skeletal muscle loss and nutritional status of patients.\(^4\)

Several tumor factors including the TNM staging system are powerful predictors of survival in gastric cancer patients treated with surgery; however, it is insufficient in reflecting the heterogeneity of the clinical course. A number of patient variables such as age, performance status, and neutrophil/lymphocyte ratio have been identified as prognostic factors for overall survival in the last decade.\(^5\)–\(^7\). Recently, the prognostic value of preoperative sarcopenia and nutritional status have been gaining emphasis.\(^8\)–\(^9\). However, we have been impressed that progressive skeletal muscle loss after gastrectomy might also be a powerful prognostic indicator based on thousands of cases of practice in our dedicated gastric cancer center. Especially, it seems that the muscle loss at one year after surgery, when adjuvant chemotherapy is completed, might be particularly important to indicate overall health state and prognosis of patients.

Thus, we hypothesized that the progressive muscle loss during the first postoperative year is a significant predictor of overall survival along with preoperative sarcopenia and nutritional status in patients with stage 2 or 3 gastric cancer who survived longer than one year. To evaluate our hypothesis, we performed this large-scale study with the aid of artificial intelligence techniques to measure body composition.

Methods

The protocol for this retrospective and registry-based cohort study was approved by the institutional review board of Asan Medical Center, Seoul, Korea (IRB No. 2017-0216). This study was reported according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) guidelines.\(^10\)

Patient selection

The current study was conducted on the basis of a comprehensive and prospectively built gastric cancer surgery registry containing the demographic characteristics of patients, preoperative evaluation results, surgery-related and postoperative outcomes, pathologic information, and follow-up data. From the registry, the data of 9,940 patients who received surgery for biopsy-proven primary gastric cancer from 2007 to 2012 at Asan Medical Center, Seoul, Korea were initially extracted. Subsequently, we included patients based on specific inclusion and exclusion criteria.

The inclusion criteria were as follows: (a) patients who were treated with curative gastrectomy followed by adjuvant chemotherapy for stage 2 and 3 gastric cancer based on the American Joint Committee on Cancer 7th edition\(^11\), (b) patients aged between 18 and 85 years, (c) patients who abide
by a regular follow-up protocol with available data on demographic measures, laboratory findings, and abdominopelvic computed tomography (CT) images. Patients (a) who died within one year after surgery, (b) who received neoadjuvant treatment, (c) with a history of previous partial gastrectomy, (d) with any synchronous malignancy in another organ, and (e) with inappropriate clinical or radiologic data were excluded. The patient selection process is illustrated in Fig. 1.

Medical data collection and follow-up
The preoperative clinicopathologic characteristics of the patients, including age, sex, body weight, height, body mass index (BMI), and history of any synchronous malignancy or comorbidity, were evaluated. Information about the type of operation (open vs. laparoscopic approach), type of gastrectomy (distal vs. total gastrectomy), and pathologic data including Lauren’s classification \(^{12}\) and tumor stage were collected from the registry. Laboratory parameters such as serum protein and albumin at preoperative and postoperative periods were extracted from the registry. The nutritional risk index (NRI) was calculated based on the formula \(1.519 \times \text{serum albumin g/L} + 0.417 \times (\text{present weight} / \text{usual weight}) \times 100\). The difference in NRI (dNRI) between before and one year after surgery was assessed. Body weight and BMI were measured at all visits. Recurrence was evaluated by serum tumor marker measurement, endoscopy, and abdominopelvic CT following the guidelines for gastric cancer treatment \(^{14}\).

Assessment of body composition
CT scans obtained before and one year after surgery were selected for body morphometric analysis. Body composition was assessed with abdominopelvic CT using an automated artificial intelligence software (AID-U™, IAID Inc., Seoul, Korea), which was developed using a fully convolutional network (FCN) segmentation technique \(^{15}\). A specialized abdominal radiologist (K.W.K), who was blinded to the clinical information, selected the axial CT slice at the L3 vertebral inferior endplate level in a semi-automatic manner with the aid of coronal reconstructed images. Then, the chosen images were automatically segmented to generate the boundary of total abdominal muscles. The skeletal muscle area (SMA) including all muscles on the selected axial images, i.e., psoas, paraspinal, transversus abdominis, rectus abdominis, quadratus lumborum, and internal and external obliques, were demarcated using predetermined thresholds (-29 to +150 Hounsfield units). The visceral fat area (VFA) and subcutaneous fat area (SFA) were also demarcated using fat tissue thresholds (-190 to -30 Hounsfield units) (Supplementary Fig. 1). The SMA was adjusted for the square of the height (SMA/height\(^2\)), which is referred to as the skeletal muscle index (SMI) \(^{16}\). The differences in SMA and SMI between before and one year after surgery were calculated to yield dSMA and dSMI, respectively.

Statistical analysis
Continuous data were reported as means with standard deviations, and categorical data were presented as proportions. Normality was assessed using frequency histograms and the Kolmogorov-Smirnov test. A paired t-test was used to compare preoperative with postoperative body composition and nutritional parameters. Overall survival was defined as the time interval between the date of diagnosis and the date of patient’s death from any cause. Patients were censored at five years for overall survival if they were alive at five years after surgery. Follow-up loss and recurrence were also regarded as censoring.

The primary endpoint of this study was to determine prognostic factors to predict overall survival in patients who lived longer than 1 year after gastrectomy. A Cox proportional hazards model was used for univariate and multivariate analyses, and outcomes were reported as hazards ratios and 95% confidence intervals. The covariates that were significant in univariate analysis were included in multivariate one. In multivariate analysis, the backward stepwise elimination method was used to determine the final significant predictors after confirming that there was no significant multicollinearity between variables by examining the correlation matrices.

The secondary endpoint was to evaluate predictive performance of the progressive muscle loss (dSMI) and preoperative nutritional status (NRI) to predicting mortality. Patients were dichotomized (high-risk vs. low-risk group) according to the median value of dSMI and preoperative NRI. Survival curves were estimated for each group using the Kaplan-Meier method and compared statistically using the log rank test. Logistic regression analysis with Enter model was carried out to assess the performance of dSMI and NRI of predicting patient mortality, and the performance was evaluated with receiver operating characteristic (ROC) curves and area under the curves (AUCs).

As a subgroup analysis, all these statistical analyses were performed in a recurrence group. P-value of < 0.05 was used as the level of significance for the study. Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and IBM SPSS® version 26 (IBM, Armonk, NY, USA).

Results
Baseline characteristics
Among the initial 9,940 patients who were registered in the gastric cancer surgery registry, there were 1,750 patients with stage 2 or 3 gastric cancer who were treated with gastrectomy followed by adjuvant chemotherapy. After excluding those who had inappropriate imaging or incomplete follow-up data (\(n = 719\)) and who died within one year after surgery (\(n = 73\)), a total of 958 patients were included in the study. As seen in Table 1, we divided patients into a recurrence group (\(n = 293\)) and a non-recurrence group (\(n = 665\)), because the treatment and prognosis of two population
differ significantly. Only distribution of tumor stage was different between two groups; tumors with an advanced stage were more frequently observed in patients experiencing relapse. The other variables did not differ significantly between the two groups.

Table 1

| Variables                        | Whole patients (N = 958) | Recurrence group (N = 293) | Non-recurrence group (N = 665) |
|----------------------------------|--------------------------|----------------------------|--------------------------------|
| Mean age at operation, years (+ SD) | 57.0 (± 12.3)          | 57.7 (± 12.6)             | 56.7 (± 12.2)                 |
| Sex                              | 624 (65.1%)             | 196 (66.9%)               | 428 (64.4%)                   |
| Male                             | 334 (34.9%)             | 97 (33.1%)                | 237 (35.6%)                   |
| Female                           | 138 (14.4%)             | 44 (15.0%)                | 94 (14.1%)                    |
| Comorbidity                      | 268 (28.0%)             | 82 (28.0%)                | 186 (28.0%)                   |
| Diabetes                         | 102 (10.6%)             | 23 (7.8%)                 | 79 (11.9%)                    |
| Others                           | 856 (89.4%)             | 270 (92.2%)               | 586 (88.1%)                   |
| Type of operation                | 549 (57.2%)             | 149 (50.9%)               | 400 (60.2%)                   |
| Laparoscopy                      | 409 (42.8%)             | 144 (49.1%)               | 265 (39.8%)                   |
| Open                             | 199 (20.8%)             | 26 (8.9%)                 | 173 (26.0%)                   |
| Type of gastrectomy              | 237 (24.7%)             | 61 (20.8%)                | 176 (26.5%)                   |
| Distal gastrectomy               | 194 (20.3%)             | 47 (16.0%)                | 147 (22.1%)                   |
| Total gastrectomy                | 194 (20.3%)             | 80 (27.3%)                | 114 (17.1%)                   |
| TNM stage*                       | 134 (14.0%)             | 79 (27.0%)                | 55 (8.3%)                     |
| 2A                               |                          |                            |                               |
| 2B                               |                          |                            |                               |
| 3A                               |                          |                            |                               |
| 3B                               |                          |                            |                               |
| 3C                               |                          |                            |                               |

*TNM stage was based on the American Joint Committee on Cancer 7th edition

Among patients, 42.4% had comorbidity and 89.4% received open surgery. Distal gastrectomy was more frequently performed than total gastrectomy (57.2% versus 42.8%) (Table 1).

Change in body composition and nutritional parameters

Body weight diminished during the first postoperative year (mean loss of 5.9 kg). All parameters related to body composition (SMA, SMI, SFA, VFA) and NRI measured at one year after surgery showed a significant decrement compared with preoperative values as well (Table 2). These changes were consistently observed in both the recurrence group and the non-recurrence group. The representative cases were presented in Fig. 2.
Table 2
Changes in body composition and nutritional parameters measured before and 1 year after surgery

| Variables | Parameters | Whole patients (N = 958) | Recurrence group (N = 293) | Non-recurrence group (N = 665) |
|-----------|------------|--------------------------|----------------------------|--------------------------------|
|           |            | Pre          | Post-1Y       | P-value | Pre          | Post-1Y       | P-value | Pre          | Post-1Y       | P-value |
| Demographic | Weight (kg) | 62.4 (± 10.0) | 56.5 (± 9.5)  | <.001   | 62.1 (± 10.0) | 55.8 (± 9.8)  | <.001   | 62.3 (± 9.9) | 56.9 (± 9.3)  | <.001   |
|            | BMI (kg/m²) | 23.5 (± 2.9)   | 21.2 (± 2.6)  | <.001   | 23.3 (± 3.0)  | 20.9 (± 2.8)  | <.001   | 23.4 (± 2.8) | 21.3 (± 2.5)  | <.001   |
| Body composition | SMA (cm²) | 122.4 (± 29.2) | 115.3 (± 26.4) | <.001   | 120.4 (± 28.5) | 111.8 (± 25.4) | <.001   | 123.2 (± 29.4) | 117.0 (± 26.7) | <.001   |
|            | SMI (cm²/m²) | 46.6 (± 17.0)   | 44.1 (± 17.0)  | <.001   | 46.4 (± 19.4)  | 43.1 (± 18.4)  | <.001   | 46.7 (± 15.8) | 44.6 (± 16.2)  | <.001   |
|            | SFA (cm²) | 113.7 (± 57.2) | 73.8 (± 47.5)  | <.001   | 111.4 (± 59.7) | 70.8 (± 48.8)  | <.001   | 114.7 (± 56.0) | 75.3 (± 46.9)  | <.001   |
|            | VFA (cm²) | 95.6 (± 57.1)   | 39.0 (± 32.8)  | <.001   | 95.7 (± 62.9)  | 39.5 (± 35.2)  | <.001   | 95.5 (± 54.5) | 38.8 (± 31.6)  | <.001   |
| Nutritional | NRI | 100.3 (± 7.0) | 93.0 (± 14.2)  | 0.003   | 98.9 (± 7.5)  | 92.8 (± 12.5)  | 0.014   | 100.9 (± 6.7) | 93.0 (± 14.9)  | 0.010   |
|            | Protein | 6.7 (± 0.6)   | 7.0 (± 0.6)    | <.001   | 6.6 (± 0.7)  | 6.9 (± 0.7)   | <.001   | 6.7 (± 0.6)  | 7.1 (± 0.5)   | <.001   |
|            | Albumin | 3.9 (± 0.5)   | 3.9 (± 0.4)    | <.001   | 3.8 (± 0.5)  | 3.8 (± 0.5)   | <.001   | 3.9 (± 0.4)  | 4.0 (± 0.4)   | <.001   |

Abbreviations: Pre, preoperative; Post-1Y, postoperative one year; BMI, body mass index; SMA, skeletal muscle area; SMI, skeletal muscle index, SMA/height²; SFA, subcutaneous fat area; VFA, visceral fat area; NRI, nutritional risk index

Prognostic relevance of skeletal muscle loss and NRI

Univariate and multivariate cox-hazard regression analysis results were presented in Table 3. In univariate analysis, the recurrence was the strongest prognostic indicator (HR 13.992). Among the clinicopathologic variables, old age, male sex, comorbidity, advanced tumor stage, open surgery, total gastrectomy, and larger tumor size were associated with a shorter survival period in patients with stage 2 and 3 gastric cancer. Among preoperative body composition and nutrition related parameters, SMA, SFA, and NRI affected prognosis. Among the parameters for body composition and nutrition change between before and one year after surgery, dSMA and dSMI were predictive of overall survival.
Table 3
Cox proportional hazards regression analyses of overall survival

| Variables          | Whole group (N = 958) | Recurrence group (N = 293) |
|--------------------|-----------------------|-----------------------------|
|                    | Univariate analysis   | Multivariate analysis       | Univariate analysis | Multivariate analysis |
| Clinicopathologic  | HR 95% CI P-value     | HR 95% CI P-value           | HR 95% CI P-value  | HR 95% CI P-value    |
| Age                | 1.019 1.011–1.028     | <0.001                      | 1.002 0.992–1.012 | 0.701                |
| Sex (male)         | 1.242 1.007–1.531     | 0.043                       | 1.009 0.785–1.297 | 0.943                |
| BMI                | 0.968 0.351–1.001     | 0.061                       | 0.999 0.960–1.039 | 0.955                |
| Comorbidity        | 1.258 1.110–1.427     | <0.001                      | 1.006 0.854–1.186 | 0.940                |
| TNM stage (stage 3)| 1.927 1.573–2.362     | <0.001                      | 1.298 1.035–1.629 | 0.024                |
| Operation type (open) | 1.458 1.027–2.072 | 0.035                       | 1.308 0.845–2.024 | 0.229                |
| Gastrectomy type (total) | 1.240 1.020–1.506 | 0.030                       | 1.109 0.875–1.405 | 0.393                |
| Tumor size         | 1.079 1.052–1.108     | <0.001                      | 1.022 0.990–1.055 | 0.173                |
| Tumor location     | 1.058 0.949–1.181     | 0.310                       | 1.033 0.921–1.159 | 0.575                |
| Lauren's classification | 0.929 0.814–1.060 | 0.272                       | 1.245 1.073–1.445 | <0.001               |
| Recurrence         | 13.992 11.197–17.486 | <0.001                      | 16.684 12.975–21.454 | <0.001               |
| Preop. Body/Nutrition |                  |                              | NA NA NA NA NA NA |
| SMA                | 0.951 0.925–0.978     | <0.001                      | 1.000 0.996–1.005 | 0.851                |
| SMI                | 1.000 0.994–1.006     | 0.965                       | 1.001 0.995–1.007 | 1.001                |
| SFA                | 0.997 0.995–0.999     | <0.001                      | 0.999 0.997–1.001 | 0.497                |
| VFA                | 1.000 0.998–1.002     | 0.864                       | 0.999 0.997–1.001 | 0.447                |
| NRI                | 0.960 0.948–0.973     | <0.001                      | 0.981 0.966–0.996 | <0.001               |
| Body/Nutrition change |              |                              | NA NA NA NA NA NA |
| dSMA               | 1.013 1.005–1.022     | 0.001                       | 1.016 1.007–1.026 | <0.001               |
| dSMI               | 1.043 1.019–1.066     | <0.001                      | 1.045 1.019–1.071 | <0.001               |
| dNRI               | 1.000 0.993–1.006     | 0.917                       | 1.004 0.995–1.002 | 0.406                |

Abbreviations: HR, hazards ratio; CI, confidence interval; Preop., preoperative; SMA, skeletal muscle area; SMI, skeletal muscle index; SFA, subcutaneous fat area; VFA, visceral fat area; NRI, nutritional risk index; dSMA, difference in SMA between before and one year after surgery; dSMI, difference in SMI between before and one year after surgery; dNRI, difference in NRI between before and one year after surgery

When these significant variables were included in the multivariate analysis as covariates, the recurrence was also the strongest predictor of overall survival (HR 16.684), and the presence of comorbidity, TNM stage, preoperative SMA and SFA, NRI, and dSMI remained as significant prognostic
factors. These results support our hypothesis that progressive muscle loss during the first year after gastrectomy is an independent predictor of worse prognosis (dSMI; HR 1.058) along with protective effect of preoperative muscle mass (SMA; HR 0.994) and nutritional status (NRI; HR 0.972).

As tumor recurrence was a dominant factor, we separately investigated the prognostic relevance of muscle loss in the recurrence group. In univariate analysis, in addition to tumor stage, Lauren's classification, and preoperative NRI, the dSMA and dSMI were related with survival. Notably, in multivariate analysis, the dSMA (HR 1.048) and dSMI (HR 0.970) maintained their significances as independent prognostic indicators of overall survival along with Lauren's classification.

**Performance of skeletal muscle loss and NRI as prognostic stratifiers**

Patients were dichotomized (high-risk vs. low-risk group) according to the median value of preoperative NRI and dSMA. Kaplan-Meier curves showed that patients with a better nutritional status (higher NRI) had a significantly better prognosis (3-year overall survival rate: 84.6% vs. 72.9%, P < 0.001) (Fig. 3A). In addition, patients with less decrease of skeletal muscle (smaller dSMI) also demonstrated longer survival period (3-year overall survival rate: 85.6% vs. 74.5%, P = 0.009) (Fig. 3B). In a subgroup analysis with the relapse group, a significant survival difference was observed between high-risk group and low-risk group for both NRI (3-year overall survival rate: 51.0% vs. 35.6%, P = 0.003) and dSMI (53.2% vs. 35.0%, P = 0.006) (Fig. 3C and 3D).

Next, we evaluated two factors' performance in mortality prediction with a logistic regression model. For all patients with stage 2 and 3 gastric cancer, a prediction model consisting of preoperative NRI and dSMI exhibited an AUC of 0.63 (P < 0.001). Subsequently, clinical factors including recurrence, tumor stage, and comorbidity which were significant in multivariate analysis were combined to the prediction model, and the AUC was increased to 0.90 (sensitivity 76.5%, specificity 94.7%, P < 0.001) (Fig. 4A).

In the recurrence group, a combined model with Lauren's classification exhibited an AUC of 0.75 (sensitivity 55.6%, specificity 88.2%, P = 0.005); however, the individual performance of preoperative NRI or dSMI was not significant (Fig. 4B).

**Discussion**

In this study, the multivariate Cox-hazard regression results supported our hypothesis that the one-year loss of skeletal muscle after gastrectomy (dSMI) is a significant predictor of overall survival along with preoperative muscle mass (SMA) and nutritional status (NRI) in stage 2 or 3 gastric cancer patients who survived longer than one year. Although several powerful prognostic factors for overall survival including recurrence, TNM stage, and comorbidity (HRs, 16.684, 1.298, and 1.262, respectively) were included in the multivariate analysis, the dSMA (HR 0.994) and preoperative SMA (HR 0.972) eventually remained as independent predictors. Kaplan-Meier curves also showed that less degree of postoperative muscle loss (small dSMA) and a better nutritional status before surgery (NRI) had a protective effect on the survival. The prognostic value of the two variables were maintained even in patients with relapsed tumor.

Nowadays, progressive loss of skeletal muscle mass has been highlighted as a prognostic factor in cancer patients, which is associated with cancer cachexia. Indeed, cachexia significantly contributes to mortality in patients with malignancy, accounting for more than 20% of cancer deaths. Especially, in patients with gastric cancer, sarcopenia is known to be highly prevalent, and a marked reduction in the initial body weight and muscle mass during the first postoperative year closely mimics the malnutrition and cancer cachexia cascade. Although several studies have reported preoperative sarcopenia as an indicator of poor prognosis, it may not reflect the steep deterioration after gastrectomy.

Our study, as a large-scale research, demonstrated that progressive muscle loss during the first year after gastrectomy is also a significant indicator of worse prognosis. Indeed, in a recent study based on a randomized multicenter trial, a marked loss in muscle or subcutaneous(visceral fat at 6 months after surgery could predict poor prognosis in patients with stage 2/3 gastric cancer. Although the study had a small number of population including patients not receiving adjuvant treatment, their results also demonstrated the prognostic importance of progressive muscle loss after gastric cancer surgery.

In terms of nutritional status, the preoperative NRI revealed its prognostic value in the recurrence group as well as whole patients. This result coincides with prior studies demonstrating that preoperative malnutrition could influence cancer-related or -unrelated death in malignancies. In contrast to our expectation, the change in NRI between before and one year after surgery (dNRI) did not influence the overall survival in gastric cancer patients. It might be attributed to the albumin homeostasis to balance albumin synthesis and catabolism or an active educational program instructing high-protein diet after surgery. However, our results should not hamper the importance of nutritional support for patients with gastric cancer.

Among several prognostic factors which were significant in this study, the dSMA and preoperative NRI could be valuable indicators because they have potentials to improve prognosis through efforts to enhance the nutritional status before surgery or maintain the muscle mass with intensive exercise and nutritional support after gastrectomy. Recently, exercise and physical activities during cancer treatment has been greatly emphasized in various malignancies, and the therapeutic benefit of exercise interventions on cancer patients have been investigated. In addition, in 2020, the American Cancer Society guidelines has been issued for diet and physical activity for cancer patients.
Only patients with stage 2 and 3 gastric cancer were included in the study because there is a discrepancy in treatment strategy and prognosis between stage 1 tumors and more advanced cancers. The vast majority of patients with stage 1 gastric cancers are treated with surgery alone and have an excellent prognosis of 5-year overall survival rate reaching to 95%. However, stage 2 and 3 cancers are indicated to surgery followed by chemotherapy, yielding the 3-year overall survival rate of 80.0%, and a significant number of patients experience relapse despite of adjuvant treatment \(^{29,30}\). In this perspective, the prognostic implication of body composition and nutrition becomes higher in stage 2 and 3 gastric cancer.

We acknowledge that this study has some limitations. First, although data were collected prospectively in the registry, this is a retrospective study based on data from a single institution. Second, as we excluded patients who died within 1 year postoperatively, the prognostic effect of skeletal muscle loss was applicable to patients who survived longer than 1 year after surgery. Finally, despite prognostic relevance, the therapeutic benefit of efforts to support nutrition and preserve muscle mass was not proven. To overcome these limitations, a well-designed prospective multi-institutional study is required. Nevertheless, this study provides robust real-world evidence which is obtained from the large-scale study composed of 958 gastric cancer patients.

**Conclusions**

Progressive muscle loss at one year after gastrectomy and preoperative NRI as well as skeletal muscle mass before surgery could be significant predictors of overall survival in patients with stage 2 or 3 gastric cancer. These evidences strongly support current trend which emphasizes proactive intervention such as preoperative and postoperative exercise and nutritional support for better outcome.

**Abbreviations**

AUC: Area under curve; BMI: Body mass index; CI: Confidence interval; CT: Computed tomography; HR: Hazard ratio; NRI: Nutritional risk index; dNRI: difference in nutritional risk index; ROC: Receiver operating characteristic; SMA: Skeletal muscle area; SMI: Skeletal muscle index; dSMI: difference in skeletal muscle index; SFA: Subcutaneous fat area; VFA: Visceral fat area

**Declarations**

**Ethics approval and consent to participate**

The protocol for this retrospective and registry-based cohort study followed the Helsinki declaration and was approved by the institutional review board of Asan Medical Center, Seoul, Korea (IRB No. 2017-0216). Informed consent was obtained in all participants in the study.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets used and analysed during this study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

KK: conception of the study, interpretation of data, creation of automated artificial intelligence software to assess muscle-fat measurement, drafting the work

KL: conception of the study, acquisition and interpretation of data, drafting the work

JL: conception of the study, analysis and interpretation of data

TP: acquisition of data imaging, analysis and interpretation of data

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CK: acquisition and analysis of data, drafting the work
JY: drafting the work, substantial revision
BK: drafting the work, substantial revision
IL: conception of the study, interpretation of data, drafting the work, substantial revision

All authors read and approved the final manuscript.

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