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Skeletal muscle gauge prediction by a machine learning model in patients with colorectal cancer

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ABSTRACT

Objectives: Skeletal muscle gauge (SMG) was recently introduced as an imaging indicator of sarcopenia. Computed tomography is essential for measuring SMG; thus, the use of SMG is limited to patients who undergo computed tomography. We aimed to develop a machine learning algorithm using clinical and inflammatory markers to predict SMG in patients with colorectal cancer.

Methods: The least absolute shrinkage and selection operator regression model was applied for variable selection and predictive signature building in the training set. The predictive accuracy of the least absolute shrinkage and selection operator model, defined as linear predictor (LP)-SMG, was compared using the area under the receiver operating characteristic curve and decision curve analysis in the test set.

Results: A total of 1094 patients with colorectal cancer were enrolled and randomly categorized into training (n = 656) and test (n = 438) sets. Low SMG was identified in 142 (21.6%) and 90 (20.5%) patients in the training and test sets, respectively. According to multivariable analysis of the test sets, LP-SMG was identified as an independent predictor of low SMG (odds ratio = 1329.431; 95% CI, 271.684–7667.996; $P < .001$). Its predictive performance was similar in the training and test sets (area under the receiver operating characteristic curve = 0.846 versus 0.869; $P = .427$). In the test set, LP-SMG had better outcomes in predicting SMG than single clinical variables, such as sex, height, weight, and hemoglobin.

Conclusions: LP-SMG had superior performance than single variables in predicting low SMG. This machine learning model can be used as a screening tool to detect sarcopenic status without using computed tomography during the treatment period.

Introduction

Muscle impairment, a condition characterized by progressive loss of muscle mass and quality, is an outstanding predictive factor for clinical outcomes in various types of cancers [1,2]. For instance, it has been reported that sarcopenia is associated with reduced response rate to chemotherapy and worse progression-free survival in lung cancer [3]. In addition, sarcopenia, along with diminished muscle strength, predicted overall survival (OS) in head and neck cancer patients compared with other variables [4]. Furthermore, sarcopenia was associated with higher surgical and medical complication rates as well as reduced functional well-being in colorectal cancer (CRC) patients [5,6]. Skeletal muscle index (SMI) and skeletal muscle radiodensity (SMD) are two values commonly used for assessing sarcopenia risk; they signify quantitative and qualitative measures of muscle composition, respectively. Recently, skeletal muscle gauge (SMG), which is defined as the product of SMI and SMD, has emerged as a noteworthy predictor of postoperative outcome in patients with cancer [7–10]. Average SMG was significantly lower in patients with grade 3 or 4 toxicity to chemotherapy than in those without grade 3 or 4 toxicity in either metastatic or early-stage breast cancer [8,9]. Our group recently reported that low SMG was an independent poor prognostic factor for OS (training set, hazard ratio = 2.18; 95% CI, 1.43–3.32; $P < .001$ and test set, hazard ratio = 1.79; 95% CI, 1.07–3.00; $P = .025$) in patients with CRC [11]. Based on these findings, we speculated that SMG might have enhanced prognostic value in comparison with SMI or SMD alone in patients with cancer.

Muscle mass and/or quality can be measured using several modalities, such as dual-energy x-ray absorptiometry, bioelectrical impedance analysis, computed tomography (CT), and magnetic

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resonance imaging [12,13]. Nowadays, CT is the most commonly used imaging modality to simultaneously assess muscle mass and quality, especially in cancer patients. However, CT use is limited because of its labor-intensive, cost-inefficient nature as well as significant radiation exposure [14]. Previous research has verified that serial changes in muscle mass are more meaningful in predicting clinical outcomes than single-stage measurements [15–17]. Considering such findings, a method that can easily predict muscle changes at various stages of treatment without resorting to CT use would be invaluable.

Several previous studies have predicted muscle impairment using only clinical values. For instance, a prognostic nomogram consisting of age, sex, body mass index (BMI), hemoglobin, and gait speed has been developed to predict low muscle mass (SMI) and radiodensity (SMD) in patients with gastric cancer [18]. An association between systemic inflammation and increased risk of sarcopenia has been previously reported; cytokines, such as tumor necrosis factor α, interleukin-6, and interleukin-1, have been implicated as promoting inflammatory cell infiltration into muscles [19]. Also, the NLRP3 inflammasome and relevant cellular pathways, including pyroptosis, have been noted to accelerate muscle dysfunction [20] As such, inflammatory markers have also been frequently used in sarcopenia risk predictive models. Since an association between systemic inflammation and increased risk of sarcopenia has been reported, inflammatory markers have also been used in sarcopenia risk predictive models. Borges et al. [21] reported that a high neutrophil-to-lymphocyte ratio (NLR) could predict sarcopenia with a sensitivity of 49% and specificity of 81.1%, suggesting an NLR of 6.5 as an optimal cutoff value. Other systemic inflammation-related variables, such as platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR), have emerged as potential predictors of sarcopenia. For instance, Yoon et al. [22] generated a machine learning model that included changes in the NLR (%/50 d) and PLR (%/50 d) to predict muscle loss during chemoradiotherapy in patients with esophageal cancer. However, only a few studies that use machine learning models dependent on systemic inflammatory markers to predict sarcopenia in patients with CRC have been conducted.

Thus, the aim of this study was to develop a machine learning model that uses routinely examined clinical variables and systemic inflammatory markers to predict SMG and ultimately anticipate the risk of muscle impairment in patients with CRC.

Methods

Patient selection

Patients with CRC treated between January 2005 and April 2014 were initially considered for this study. Patients without the following information were excluded from the analysis: cell type, tumor location, tumor stage, preoperative treatment, SMD, SMI, NLR, and albumin-bilirubin (ALBI) score. In addition, patients with hereditary colon cancer, ulcerative colitis or Crohn's disease–associated cancer, double primary cancer, or inflammatory bowel disease were excluded along with those who underwent emergency surgery, those whose CT images were not taken ≤31 d before surgery, and those whose NLR values were not measured ≤31 d from surgery (Supplementary Fig. 1).

This study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Informed consent was waived because of the retrospective nature of the study.

Measurements of SMI, SMD using CT images, and calculation of SMG

Skeletal muscle computed tomography (CT) images were obtained at the level of the third lumbar vertebra. Skeletal muscle area (SMA) was measured by inserting cross-sectional L3 CT images into the open-source software BMI_CT (https://sourceforge.net/projects/muscle-fat-area-measurement) [23]. SMD was measured using 3D Slicer, another open-source software (https://www.slicer.org/) [24]. Two investigators determined the intraclass correlation coefficients of SMI and SMD using the aforementioned software, yielding values of 0.97 (range = 0.95–0.99) and 0.99 (0.97–0.99), respectively, as in our previous study [25]. Hounsfield units (HU) ranging from −29 to +150 were used to measure SMA (cm^2), which was then normalized for height to obtain the SMI values (cm^2/m^2). SMD was calculated as the mean HU of SMA. SMG was obtained by calculating the product of SMI and SMD values as suggested by Weinberg et al. [7]. As numerous studies have been conducted, we used an arbitrary unit (AU) instead of ($cm^2 \times HU/m^2$) for SMG for simplicity. The optimum cutoff value of SMG in patients with CRC was chosen by observing associations with OS, as in our previous study [11]. Accordingly, 1640 and 1523 AU were used as cutoff values for men and women, respectively.

Generation and validation of LASSO-based linear predictor skeletal muscle gauge

Patients were assigned to the training and test sets via randomization. Using variables, such as sex, age, and BMI, a linear predictor (LP) was generated using least absolute shrinkage and selection operator (LASSO) regression, a method widely used to eliminate variables of minimal significance while retaining those with sufficient influence in the course of prediction. By applying this method, variable selection and predictive signature building were performed, and coefficient estimates were reduced to zero, where such shrinkage was dependent on the parameter λ. Cross-validation was performed 10 times to obtain the optimal values of λ, during which the minimum criteria were used. Subsequently, the predictive prowess of the model obtained via LASSO regression was analyzed by comparing the area under the receiver operating characteristic (AUROC) curve and the area under curve precision recall and performing decision curve analysis in the test set.

Statistical methods

Variance tests were used to analyze clinicopathologic characteristics. To compare categorical variables, the χ^2 test or Fisher's exact test was used, whereas Student's t test or Mann-Whitney U test was used to compare continuous variables. Univariable analyses were performed to obtain the odds ratios (ORs) of the single variables in the logistic regression (LR) model, which found the association between each variable and low SMG via one-to-one matching. Multivariable analysis was used to select factors associated with low SMG via backward selection. AUROC curve values were compared using the DeLong test. A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed using R version 4.2.0 (R Project, Institute for Statistics and Mathematics, Vienna, Austria).

Results

Patient characteristics and clinicopathologic features

A total of 1642 patients with CRC were initially considered, and 1094 patients met the inclusion criteria and were included in the

Table 1
Comparison of clinicopathologic variables between the training and test set (n = 1094)

Variables	Subcategory	Training set (n = 656) N (%)	Test set (n = 438) N (%)	P
Sex	Male	378 (57.6)	267 (61)	
	Female	278 (42.4)	171 (39)	0.300
Age (y)	Mean (SD)	62.4 (11.9)	62.7 (11.7)	0.706
Height (m)	Mean (SD)	1.6 (0.1)	1.6 (0.1)	0.844
Weight (kg)	Mean (SD)	61.6 (10.6)	62 (10)	0.530
BMI (kg/m^2)	Mean (SD)	23.3 (3)	23.4 (3.1)	0.402
Smoking	No	437 (66.6)	314 (71.7)	
	Yes	219 (33.4)	124 (28.3)	0.088
DM	No	530 (80.8)	362 (82.6)	
	Yes	126 (19.2)	76 (17.4)	0.487
HTN	No	377 (57.5)	253 (57.8)	
	Yes	279 (42.5)	185 (42.2)	0.973
Tumor location	colon	476 (72.6)	309 (70.5)	
	rectum	180 (27.4)	129 (29.5)	0.512
NLR	Mean (SD)	2.9 (2.6)	2.8 (2.0)	0.672
PLR	Mean (SD)	176.9 (109.1)	176.3 (84.6)	0.915
LMR	Mean (SD)	5.3 (2.3)	5.3 (2.3)	0.675
Hemoglobin	Mean (SD)	12.6 (2)	12.7 (1.9)	0.159
Albumin	Mean (SD)	4.2 (0.5)	4.2 (0.5)	0.758
ALBI score	Mean (SD)	−2.9 (0.4)	−2.9 (0.4)	0.841
SMI	Mean (SD)	48.7 (8.7)	48.1 (8.9)	0.328
SMD	Mean (SD)	42.2 (8.6)	42.7 (8.2)	0.319

ALBI, albumin-bilirubin; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index

study. The included patients were randomly divided into a training set (n = 656; 60%) and a test set (n = 438; 40%). The clinicopathologic features of patients in each set are presented in Table 1. Between the training and test sets, none of the variables, including sex, age, height, weight, and BMI, differed significantly.

Association of various factors with low SMG

A low SMG was identified in 142 (21.6%) and 90 (20.5%) patients in the training and test sets, respectively. Once the factors associated with low SMG were identified in the training set, univariable analysis was performed to assess the strength of the associations, the results of which are displayed in Table 2.

Table 2
Univariable analysis of factors associated with low skeletal muscle gauge in the training set (n = 656)

Variables	Subcategory	OR (95% CI)	P
Sex	Male vs. female	6.427 (4.235–9.970)	< 0.001
Age (y)		1.077 (1.056–1.099)	< 0.001
Height (m)		0.917 (0.896–0.939)	< 0.001
Weight (kg)		0.943 (0.924–0.961)	< 0.001
BMI (kg/m^2)		0.955 (0.898–1.016)	0.151
Smoking	No vs. yes	0.393 (0.245–0.612)	< 0.001
DM	No vs. yes	1.166 (0.727–1.829)	0.512
HTN	No vs. yes	1.368 (0.941–1.987)	0.099
Tumor location	Colon vs. rectum	0.793 (0.510–1.209)	0.292
NLR		1.003 (0.926–1.072)	0.926
PLR		1.002 (1.0004–1.003)	0.014
LMR		0.978 (0.900–1.061)	0.607
Hemoglobin		0.760 (0.687–0.837)	< 0.001
Albumin		0.383 (0.263–0.553)	< 0.001
ALBI score		2.729 (1.764–4.247)	< 0.001

ALBI, albumin-bilirubin; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLR, platelet-to-lymphocyte ratio

Generation of linear predictor of low SMG via LASSO

To obtain the LASSO-derived LP, a binomial deviance curve was plotted with the horizontal axis representing log(λ), with λ as a tuning hyperparameter, and vertical solid lines indicating binomial deviance and SE at each value of log(λ). The two vertical dotted lines represent the optimal log(λ) values obtained via the minimum criteria (left) and 1-SE criteria (right). The chosen values were those calculated using the minimum criteria, with values of λ = 0.005179939 and log (λ) = −5.262962. The optimized model was then trained with the training set, yielding 10 non-zero coefficients and the intercept of the LP-SMG (Supplementary Fig. 2).

Predictive qualities of the LP-SMG in the test set

After the identification of factors associated with low SMG and the generation of a LP via LASSO for each group, multivariable analysis was performed on the test set to assess the validity of the associations and, in particular, to verify the performance of the newly constructed LPs after accounting for interfactor effects. The factors associated with low SMG are summarized in Table 3. The LP-SMG was found to be significantly associated with low SMG even after adjusting for intervariable influence.

In addition, comparison of AUROC curve suggested that the predictability of LP-SMG was consistent between the training set and the test set, as shown in Figure 1. The relative predictive strength of the LP-SMG compared with the other variables was also verified using the AUROC curve values, as presented in Figure 2. The LP-SMG exhibited superior predictive qualities compared with these variables, as confirmed by a head-to-head comparison of AUROC curve values via the DeLong test. Furthermore, decision curve analysis found a positive net benefit against the three aforementioned variables (Fig. 3).

The performance of LP-SMG was additionally confirmed by comparison of area under curve precision recall. The area under curve precision recall value of LP-SMG (0.670; 95% CI, 0.624–0.712) was significantly higher than that of clinical variables, such as hemoglobin (0.351, 95% CI, 0.308–0.397), height (0.428; 95% CI, 0.382–0.475), and sex (0.367; 95% CI, 0.323–0.413) (Supplementary Fig. 3, Supplementary Table 1).

Optimal cutoff value of LP-SMG

The cutoff value for LP-SMG in predicting low SMG in the test set was 0.269 (Supplementary Fig. 4, Supplementary Table 2). Using this cutoff value, the actual counts and rates of SMG in the test set were compared with the respective predicted values. Both

Table 3
Multivariable analysis of factors associated with low skeletal muscle gauge in the test set (n = 438)

Variables	Subcategory	OR (95% CI)	P
Sex	Male vs. female	—	
Age (y)		—	
Height (m)		—	
Weight (kg)		—	
Smoking	No vs. yes	—	
PLR		—	
Hemoglobin		0.802 (0.665–0.967)	0.078
Albumin		0.636 (0.347–1.167)	0.146
ALBI score		—	
LP-SMG		1329.431 (271.684–7667.996)	< 0.001

ALBI, albumin-bilirubin; OR, odds ratio; PLR, platelet-to-lymphocyte ratio

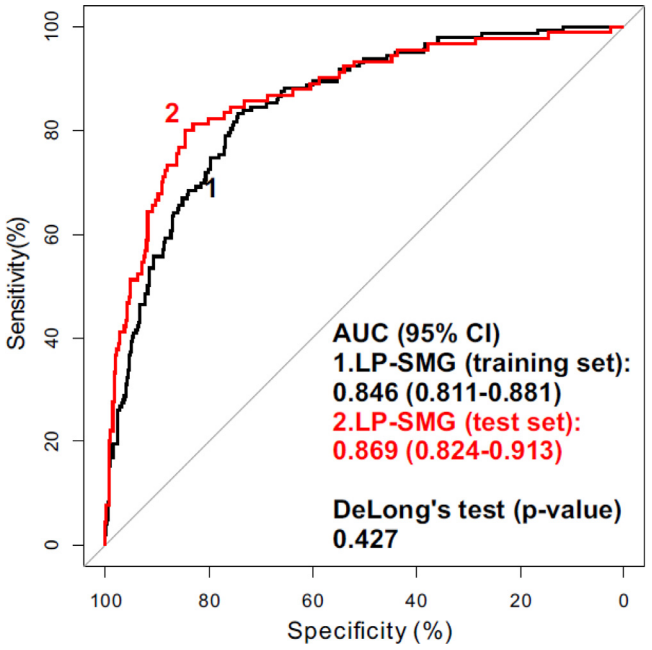

Fig. 1. Comparison of AUROC curve value of LP-SMG in the training and test set. The AUROC of LP-SMG was 0.846 (95% CI, 0.811–0.881) in the training set and 0.869 (95% CI, 0.824–0.913) in the test set (P = .427). AUROC, area under the receiver operating characteristic; LP-SMG, linear predictor skeletal muscle gauge.

high and low SMG were predicted with considerable accuracy by LP-SMG in the test set (Supplementary Fig. 5).

Discussion

In this study, we developed a LASSO regression-based machine learning model to predict low SMG. This model, the LP-SMG, had high performance, with AUROC curve values of 0.846 and 0.869 in the training and test sets, respectively. Moreover, it estimated low SMG with enhanced precision than other clinical parameters, such as sex, height, weight, and hemoglobin. Decision curve analyses also supported this result, having a higher net benefit for LP-SMG. To the best of our knowledge, this is the first study to suggest a machine learning model that can predict SMG from clinical variables. Our study highlights the possibility of adopting sarcopenic status as a simple tool for close and cost-effective patient monitoring, while reducing the need for frequent CT scans in patients with CRC.

SMI and SMD are the skeletal muscle–related indices most significantly associated with clinical outcomes in patients with cancer. Patients with sarcopenia classified as having low SMI had a significantly higher risk of postoperative complications and reduced OS [26–30]. Myosteatosis, most widely diagnosed by low SMD in CT images, is also known to be a powerful negative prognostic indicator for various types of cancer [31–33]. Nevertheless, it is labor-intensive, cost-inefficient, and, ultimately, not viable to perform frequent CT scans to measure SMI or SMD. Therefore, several attempts have been made to measure the sarcopenic status of patients without using CT. Zhang et al. [18] developed nomograms to predict low muscle mass and radiodensity in patients with gastric cancer. Logistic regression analysis was used to generate the nomogram, and it had considerable performance in predicting SMI and SMD (SMI, AUROC = 0.809; 95% CI, 0.753–0.864, and SMD, AUROC = 0.752; 95% CI, 0.694–0.810) in the validation cohort. Yoon et al. [22] investigated the effect of a machine learning–based approach and found that the ensemble model of logistic regression and a support vector classifier was the most effective, with AUROC = 0.808. In that study, changes in BMI (%/50 d), albumin (%/50 d), prognostic nutritional index (%/50 d), NLR (%/50 d), and PLR (%/50 d) were included in the model to predict muscle loss during chemoradiotherapy in patients with esophageal cancer. Although a series of studies has attempted to generate a predictive model for skeletal muscle depletion, there are persisting

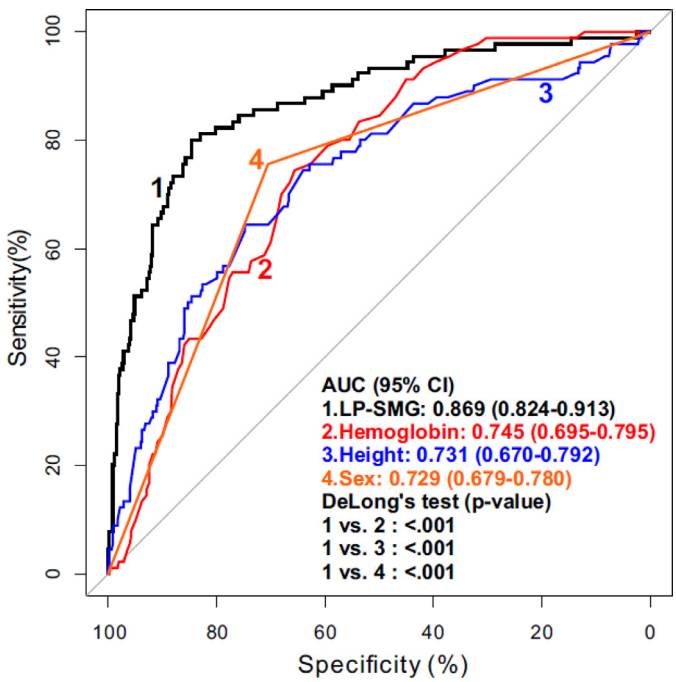

Fig. 2. Comparison of AUROC curve value between LP-SMG and clinical variables in the test set. The AUROC of LP-SMG (0.869; 95% CI, 0.824–0.913) was higher than those of hemoglobin (0.745, 95% CI, 0.695–0.795), height (0.731; 95% CI, 0.670–0.792), and sex (0.729; 95% CI, 0.679–0.780), indicating stronger predictability. AUROC, area under the receiver operating characteristic; LP-SMG, linear predictor skeletal muscle gauge.

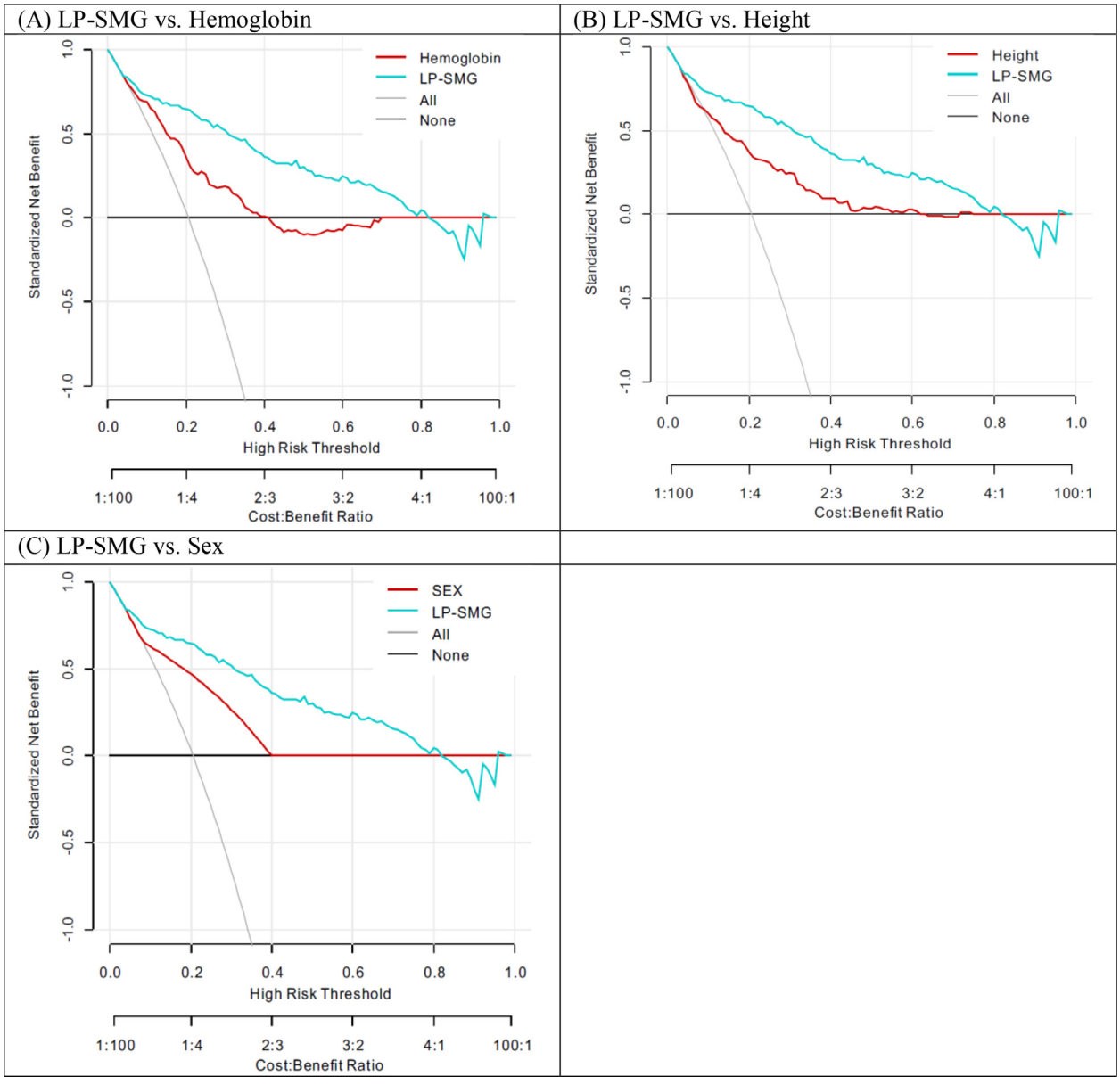

Fig. 3. Decision curve analysis between LP-SMG and clinical variables in the test set. The y-axes represent net benefit, and the x-axes represent threshold probability. The red lines represent clinical variables, namely (A) hemoglobin, (B) height, and (C) sex, while the blue lines represent LP-SMG. The curves for assumptions of treating all patients (gray lines) and no patients (black lines) are also plotted for comparison. LP-SMG, linear predictor skeletal muscle gauge. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

limitations. Some variables, such as gait speed or hand grip strength, are not commonly measured in clinical practice; additionally, the performance of the models was not substantial enough to warrant introducing the tests evaluating these variables as regular clinical practice. Although the later predictive model in patients with esophageal cancer improved performance by applying a machine learning approach, it is difficult to extend its application to other types of cancer, especially when examining change in serum markers after chemoradiation therapy.

To generate a machine learning model, we included several serum-derived markers, such as NLR, PLR, LMR, and ALBI scores. The prognostic significance of systemic inflammation was already observed in patients with CRC [34–36]. In addition, systemic inflammation mediated by various cytokines is closely related to the muscle [37]. Proinflammatory cytokines and molecules released by tumors can impair protein synthesis and muscle regeneration, leading to sarcopenia [38]. Feliciano et al. [35] reported that a greater NLR in the months before diagnosis was significantly associated with sarcopenia at diagnosis in 2470 patients with stages I to III CRC. Similarly, a recent study reported that a high NLR was associated with a high risk of sarcopenia as well as decreased hand grip strength, gait speed, calf circumference, and arm circumference [21]. The ALBI score, composed of objective parameters, such as albumin and bilirubin levels, was first suggested as a simple variable to evaluate liver function [39]. The ALBI grade determined by the ALBI score could predict the prognosis of patients with liver diseases, especially those with hepatocellular carcinoma or liver cirrhosis [40,41]. However, because liver function is deteriorated by increased proinflammatory cytokines in cancer cachexia, the ALBI score can also function as a prognostic

indicator in other patients, including those with gastric, pancreatic, and CRCs [12,42–44]. Our recent study found that SMD was considerably higher in the high ALBI group than in the low ALBI group (43.3 HU versus 37.7 HU; $P < .001$) in patients with CRC [36]. Based on these observations, we adopted the ALBI score as a significant candidate for predicting sarcopenic status.

The AUROC curve value for the prediction of SMG was obtained for each clinical parameter. We found that hemoglobin level, height, weight, and sex showed relatively higher AUROC curve values in the test set (Supplementary Table 3). The difference in mean SMG value between men and women has been reported before, indicating the relevance of sex in predicting low SMG. Because height and weight also show differences according to sex, they are thought to have correlations as well. However, the large AUROC curve value of hemoglobin is an interesting finding. Several studies have reported an association between hemoglobin and sarcopenia [45–47]. Because hemoglobin levels reflect the overall nutritional status as well as chronic energy consumption, malnutrition results in both anemia and sarcopenia, and chronic wasting in sarcopenia may accelerate the consumption of hemoglobin [47].

In our study, NLR, PLR, and LMR exhibited lower AUROC curve values than other clinical parameters. According to a previous study on 123 hospitalized cancer patients, NLR had a sarcopenia predictability (AUROC = 0.61; 95% CI, 0.51–0.68) superior to that reported in our study [21]. Another prospective study of 670 patients with gastric cancer who underwent radical gastrectomy also showed a sarcopenia predictive ability of NLR (AUROC = 0.663; 95% CI, 0.603–0.723) and PLR (AUROC = 0.655; 95% CI, 0.598–0.712) greater than those found in our study [48]. Although the exact reason for this discrepancy is unclear, different criteria of sarcopenia among the studies, different characteristics of the included patients, and cancer types might have affected the results. Further analysis of the mechanisms underlying these differences should be tackled in future studies.

Our model has several merits. First, it is not contingent on sex, making it easier to apply. Second, our predictive model is feasible because it only requires routinely measured clinical variables and blood test results. These clinical and blood-derived variables are repeatedly obtained for patients with cancer. Because of these characteristics, this model can be used to postoperatively predict the sarcopenic status of patients, after chemotherapy, or during regular follow-up. Additional research is required to determine whether serial prediction using this model is clinically significant.

In this study, we focused on SMG rather than SMI or SMD. Although SMI is the most commonly used indicator of sarcopenia, a handful of studies found no difference of survival according to the classification of SMI [49–52]. Similarly, although the significance of SMD in patients with CRC was proven in our recent meta-analysis, there remains a disadvantage that the exact cutoff value of SMD is not the same for each study [32]. Based on this observation, we aimed to predict SMG, which was analyzed to be more useful in our previous study than SMI or SMD. Interestingly, when we generated additional LASSO-based prediction models using the same training and test sets, the AUROC curve values for predicting low SMI and SMD in the test set (SMI = 0.750; 95% CI, 0.695–0.804, and SMD = 0.781; 95% CI, 0.729–0.832) (data not shown) were lower than that of the LP-SMG.

This study has several limitations. Because this was a single-center retrospective study, it was difficult to avoid selection bias. The sex-specific cutoffs of SMG are still ambiguous because body composition may differ according to cachexia status, cancer type, or ethnicity. The clinical efficacy of model should also be confirmed in patients with other types of cancer or different ethnicities. Furthermore, the lack of external validation suggests a need for additional measures to generalize the results of this study. Finally, prediction of adequate sample size was a major obstacle, primarily because of the lack of similar previous studies that could be used as reference.

Conclusions

We developed an LP-SMG model for predicting sarcopenic status, which had superior performance compared with other single clinical variables. Machine learning is thought to be helpful in improving the predictive power of models assessing sarcopenic status. Our model can potentially be adopted as a screening tool to detect sarcopenic status, and applying a machine learning model might be beneficial in reducing the effort, cost, and radiation exposure from conventional CT-based diagnosis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2023.112146.

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