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Predictive scoring of high-grade histology among early-stage lung cancer patients: The MOSS score

Wongi Woo[1] | **Yoon Jin Cha**[2] | **Chul Hwan Park**[3] | **Duk Hwan Moon**[1] | **Sungsoo Lee**[1]

[1]Department of Thoracic and Cardiovascular Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

[2]Department of Pathology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

[3]Department of Radiology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

Correspondence
Sungsoo Lee, Department of Thoracic and Cardiovascular Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, South Korea.
Email: chestlee@yuhs.ac

Abstract

Background: Poor prognosis associated with adenocarcinoma of International Association for the Study of Lung Cancer (IASLC) grade 3 has been recognized. In this study we aimed to develop a scoring system for predicting IASLC grade 3 based before surgery.

Methods: Two retrospective datasets with significant heterogeneity were used to develop and evaluate a scoring system. The development set was comprised of patients with pathological stage I nonmucinous adenocarcinoma and they were randomly divided into training ($n = 375$) and validation ($n = 125$) datasets. Using multivariate logistic regression, a scoring system was developed and internally validated. Later, this new score was further tested in the testing set which was comprised of patients with clinical stage 0–I non-small cell lung cancer (NSCLC) ($n = 281$).

Results: Four factors that were related to IASLC grade 3 were used to develop the new scoring system the MOSS score; male (M, point 1), overweight (O, point 1), size>10 mm (S, point 1), and solid lesions (S, point 3). Predictability of IASLC grade 3 increased from 0.4% to 75.2% with scores from 0 to 6. The area under the curve (AUC) of the MOSS was 0.889 and 0.765 for the training and validation datasets, respectively. The MOSS score exhibited similar predictability in the testing set (AUC: 0.820).

Conclusion: The MOSS score, which combines preoperative variables, can be used to identify high-risk early-stage NSCLC patients with aggressive histological features. It can support clinicians in determining a treatment plan and surgical extent. Further refinement of this scoring system with prospective validation is needed.

KEYWORDS

adenocarcinoma, International Association for the Study of Lung Cancer, non-small cell lung cancer, prediction model, preoperative factors

INTRODUCTION

With improvements in lung cancer screening programs, the proportion of lung adenocarcinomas that are detected early has increased.[1–3] Since the histopathological subtypes of pulmonary adenocarcinomas are associated with clinical prognosis, the 2015 World Health Organization (WHO) classification designated adenocarcinomas according to their predominant patterns, which were found to have clinical implications.[4]

Recently, the International Association for the Study of Lung Cancer (IASLC) devised a new grading system based on the predominant subtypes and the number of high-grade patterns.[5] High-grade patterns include micropapillary and solid subtypes associated with aggressive tumor characteristics, as well as a complex glandular pattern, which has been classified as an acinar predominant pattern. This grading system quantitatively analyzed the impact of high-grade histological patterns and provided another tool to differentiate early-stage invasive adenocarcinoma. This IASLC grading system has also been validated in several studies, mostly involving Asian populations.[6–9] It allows prognostic stratification in terms of overall survival (OS) and recurrence-free

survival (RFS) in all cancer stages, as well as in the subgroup of stage I patients. Additionally, IASLC grade 3 has been identified as the most relevant risk factor for predicting clinical outcomes.[9,10]

As intraoperative biopsy results are often inconclusive, more extensive pulmonary resection or lymph node dissection may be required to avoid the need for additional surgery. Several studies have reported preoperative clinical and radiological variables that are predictive factors for micropapillary, solid pattern, and IASLC grade 3 cancer.[11,12] If high-grade patterns could be predicted using demographic and radiological variables, this would be important in predicting prognosis and surgical planning. It could also improve the interpretation of frozen biopsy histology between thoracic surgeons and pathologists.

Our study, therefore, aimed to devise a new scoring system to predict IASLC grade 3 based on preoperative clinical and radiological variables, using a retrospective analysis of lung cancer patients, and to validate this system by applying it in an external clinical cohort.

METHODS

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of our institution (IRB no. 3-2022-0219). The requirement for obtaining informed patient consent was waived due to the retrospective design of the study.

Study population

Our retrospective study included two cohorts with different configurations, as shown in Figure 1. The first cohort (development set, $n = 500$) included patients diagnosed with stage I pulmonary adenocarcinoma, between 2012 and 2019. Among the 716 adenocarcinoma patients identified during that period, we excluded those with adenocarcinoma in situ, mucinous adenocarcinoma, previous lung cancer history, neoadjuvant treatments, stage II–IV adenocarcinoma, an insufficient surgical margin (R1 or R2), and insufficient pathological reports, during the medical record review process. The final first cohort was then randomly divided into a training ($n = 375$) and validation ($n = 125$) dataset. The scoring system was developed based on the training dataset and then validated in this internal validation dataset.

Subsequently, to test the predictive ability of the scoring system, we used another dataset with a different composition. The second cohort (testing set, $n = 281$) consisted of patients with clinical stage 0 to I non-small cell lung cancer (NSCLC) who underwent surgery between 2020 and 2021. Among the 335 patients who underwent surgery for NSCLC, we excluded those with clinical stage II–IV NSCLC, a history of previous lung cancer, endobronchial or cavitary lesions, neoadjuvant treatments, and insufficient radiological data. Finally, 281 patients were included for external validation of the new scoring system.

Histological evaluation

All pathological slides were re-evaluated to apply the new IASLC grading system: grade 1, lepidic predominant tumors with no or less than 20% high-grade patterns (solid, micropapillary, cribriform, and/or complex glandular patterns); grade 2, acinar or papillary predominant tumors with no or less than 20% high-grade patterns; and grade 3, any tumor with 20% or more high-grade patterns.[5] Moreover, detailed pathological characteristics included visceral pleural/lymphovascular invasion and tumor spread through the air space (STAS).

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 25.0 (IBM SPSS Inc.) and R version 4·0·4 (R Core Team).

Continuous variables are presented as medians and interquartile ranges, based on the results of a normality test. The Mann–Whitney U test was used to compare differences in the defined variables. Fisher's exact test was used to compare categorical variables.[13] Logistic regression was used to determine the predictive factors for IASLC grade 3. Variables with $p < 0.10$ in univariable analysis were included in multivariable analysis, and the variables were selected by backward elimination. The scoring system for IASLC grade 3 was devised based on the following factors:

Step 1: Development and validation of the scoring system.

The cohort of patients with pathologically diagnosed stage I adenocarcinoma was randomly divided into two datasets (training and validation datasets) at a ratio of 3:1. The training dataset was used to identify variables predicting IASLC grade 3 ($p < 0.10$) from the multivariable logistic regression analysis. The score for each variable was calculated based on the adjusted odds ratio (OR) and regression coefficient. The natural logarithm of each OR was used to find regression coefficient and each of them were compared, then calculated for the score. The discriminative power of the new model was assessed by plotting a receiver operating characteristic curve and calculating the area under the curve (AUC). Predictive ability was subsequently assessed in the validation dataset in the same manner.

Step 2: Test of the scoring system.

As the training and validation cohorts consisted of only patients with adenocarcinoma diagnosed after surgery, its predictive ability prior to surgery could not be guaranteed. To test the predictive ability of the scoring system in clinical practice, the system was applied to a different cohort (the testing set) of patients with clinical stage 0 to I NSCLC who were referred for surgery during different periods. The

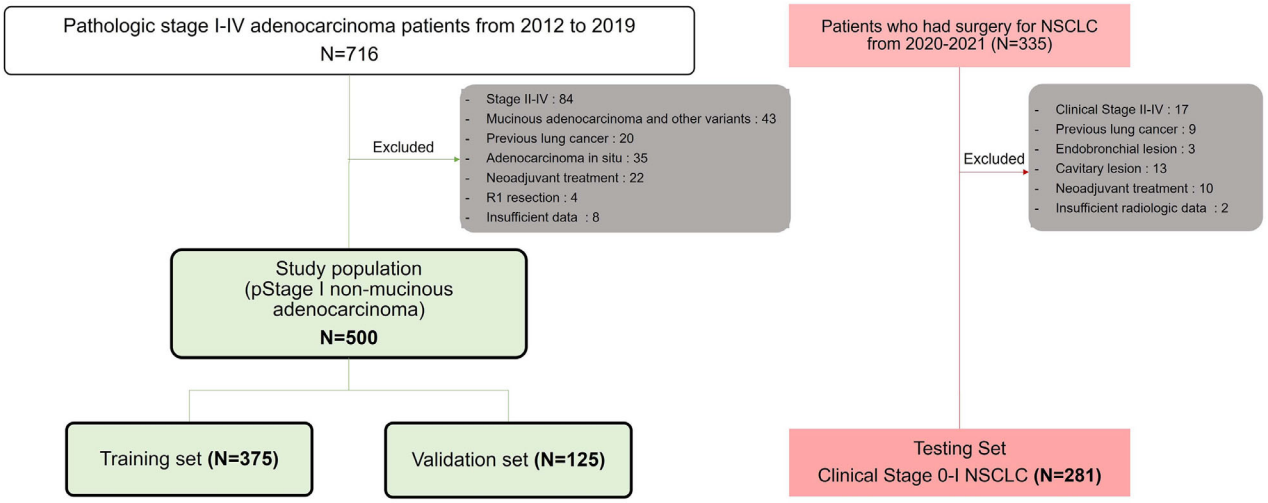

FIGURE 1 Patient selection process in this study. NSCLC, non-small cell lung cancer.

predictive performance of the new scoring system was assessed by computing the AUC.

RESULTS

Clinical characteristics of the training and validation cohorts

The study population consisted of Asians, and most were female patients (57.8%) and nonsmokers (75.2%). The patients' pulmonary function was relatively preserved, and only 2.4% of them had chronic obstructive pulmonary disease (COPD). Notably, only approximately one-third of the patients (30.2%) presented radiologically solid lesions, with a high proportion of pure ground-glass opacity (GGO) (17.0%). Among the patients (425/500, 85.0%) evaluated with positron emission tomography (PET), approximately one-third (35.8%) demonstrated no metabolic activity. There were no significant differences in preoperative variables between the training and validation datasets (Table 1).

Surgical approach and outcomes

Table 2 describes the surgical, clinical, and pathological outcomes of the patients in the two datasets. In general, 37.0% of patients underwent sublobar resection (wedge resection, 24.4%; segmentectomy, 12.6%). The 5-year OS and RFS rates from Kaplan–Meier survival curves were 90.4% and 87.6%, respectively. In terms of histopathological characteristics, 15.6% of the entire population was diagnosed with IASLC grade 3 adenocarcinoma. Although there were no differences in the surgical extent and general outcome between training and validation datasets, a greater number of IASLC grade 3 ($p = 0.012$) and STAS positivity ($p < 0.001$) were observed in the validation set than in the training set.

Risk factor analysis for the prediction of IASLC grade 3

Multivariable logistic regression analysis revealed that male sex (OR: 3.77, 95% confidence interval [CI]:1.34–10.7, $p = 0.012$), body mass index (BMI) > 25 kg/m^2, implying overweight (OR: 2.63; 95% CI: 1.18–5.87, $p = 0.018$), and pure solid lesion (OR 14.5, 95% CI: 4.90–42.9, $p < 0.001$) were significantly associated with IASLC grade 3 (Table 3). A tumor diameter >10 mm (OR: 6.04; 95% CI: 0.72–50.5; $p = 0.097$) was also included in the final scoring system, due to the clinical significance of tumor size.

The MOSS scoring system for IASLC grade 3

The MOSS score (M = male, O = overweight, S = size >10 mm, S = solid lesion) was calculated as a summation of the defined factors applied to the prediction model. Three variables (male sex, overweight, and size >10 mm) had similar weights for predicting the outcome (1 point each), whereas the fourth variable (solid lesion on computed tomography [CT]) had a greater weight (3 points) according to its OR and beta-coefficient. The MOSS score was a sum of these points. The predicted probability of IASLC grade 3 was proportional to the scores: probabilities of 0.4%, 1.1%, 5.0%, 15.0%, 31.0%, 51.0%, and 75.2%, with MOSS scores of 0, 1, 2, 3, 4, 5, and 6, respectively (Figure 2). The AUC in the training dataset was 0.889 (95% CI: 0.852–0.927), indicating good predictive ability.

TABLE 1 Preoperative characteristics of patients diagnosed with pulmonary adenocarcinoma (Development set).

	Total	Training set	Validation set	*p*-value
Variables	$N = 500$	$n = 375$	$n = 125$	
Demographic findings				
Age (years)	62.0 [54.0, 70.0]	63.0 [54.0, 71.0]	61.0 [54.0, 67.0]	0.065
Sex				0.531
Female	289 (57.8)	220 (58.7)	69 (55.2)	
Male	211 (42.2)	155 (41.3)	56 (44.8)	
BMI	23.7 [21.7, 25.7]	23.6 [21.7, 25.6]	23.7 [21.8, 25.7]	0.849
Smoking history				0.812
Never smoker	376 (75.2)	283 (75.5)	93 (74.4)	
Current or ex-smoker	124 (24.8)	92 (24.5)	32 (25.6)	
Diabetes mellitus	85 (17.0)	70 (18.7)	15 (12.0)	0.099
Hypertension	205 (41.0)	160 (42.7)	45 (36.0)	0.208
Cardiovascular diseases	38 (7.6)	31 (8.3)	7 (5.6)	0.436
COPD	12 (2.4)	8 (2.1)	4 (3.2)	1
DLCO/VA, %	108.0 [96.0, 120.0]	108.0 [96.0, 120.0]	107.0 [96.2, 120.7]	0.887
FEV1, %	108.0 [96.5, 119.0]	108.0 [96.0, 119.0]	107.0 [98.0, 116.0]	0.704
FEV1/FVC, %	75.0 [70.0, 80.0]	75.0 [70.0, 80.0]	77.0 [71.0, 80.0]	0.072
Carcinoembryonic antigen, ng/mL	2.10 [1.30, 3.30]	2.10 [1.30, 3.30]	1.90 [1.20, 3.55]	0.697
Hemoglobin, g/dL	13.2 [12.4, 14.3]	13.2 [12.4, 14.2]	13.3 [12.4, 14.4]	0.268
Location of lesions				
Lt	176 (35.2)	133 (35.5)	43 (34.4)	0.914
Rt	324 (64.8)	242 (64.5)	82 (65.6)	
Lower	176 (35.2)	137 (36.5)	39 (31.2)	0.332
Upper	324 (64.8)	238 (63.5)	86 (68.8)	
Radiological findings				
Longest diameter, mm	15.0 [10.0, 22.0]	15.00 [10.0, 22.0]	15.0 [11.0, 23.0]	0.344
Radiological types[a]				0.087
Part-solid	264 (52.8)	202 (53.9)	62 (49.6)	
Pure GGO	85 (17.0)	69 (18.4)	16 (12.8)	
Pure solid	151 (30.2)	104 (27.7)	47 (37.6)	
^{18}F-FDG uptake on PET/CT[b]				0.365
No uptake	152 (35.8)	114 (37.5)	38 (31.4)	
Moderate	112 (26.4)	81 (26.6)	31 (25.6)	
High	161 (37.9)	109 (35.9)	52 (43.0)	
Interval between CT scan and surgery, days	19.0 [9.0, 31.0]	20.0 [10.0, 32.0]	18.0 [8.0, 29.0]	0.173

Note: Data are presented as *n* (%), *n*/*N* (%), or median (interquartile range).
Abbreviations: BMI, body-mass index; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DLCO/VA, carbon monoxide diffusion capacity per unit alveolar volume; ^{18}F-FDG, 18F-fluorodeoxyglucose FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GGO, ground glass opacity; PET, positron emission tomography.
[a]Consolidation/tumor ratio (CTR) was used for classification: part solid, 0 < CTR <1; pure GGO, CTR = 0; pure solid, CTR = 1.
[b]Maximum standardized uptake value (SUV_{max}) was used for classification: Moderate, 0 < SUV_{max} <2.5; High, SUV_{max} ≥2.5.

Validation and testing of the MOSS score system

When the MOSS score was evaluated in the validation dataset, it also demonstrated good predictive ability (AUC = 0.765; Figure 3). Subsequently, the MOSS score was tested using the external validation dataset comprising patients with clinical early-stage NSCLC (testing set). The overall patient characteristics in the training/validation and testing datasets are presented in Table S1. The testing cohort did not differ from the training/validation dataset in terms of age, sex, and comorbidities, other than hypertension; however, the proportion of pure GGO and solid lesions were higher in the testing set (both $p = 0.001$) (Table S1). After surgery, approximately 86.8% of patients were diagnosed with nonmucinous adenocarcinoma, including 32 (11.4%)

TABLE 2 Surgical and pathological outcomes of patients diagnosed with pulmonary adenocarcinoma.

	Total	Training set	Validation set	*p*-value
Variables	$N = 500$	$n = 375$	$n = 125$	
Extent of surgery				0.741
Wedge resection	122 (24.4)	88 (23.5)	34 (27.2)	
Segmentectomy	63 (12.6)	49 (13.1)	14 (11.2)	
Lobectomy	314 (62.8)	237 (63.2)	77 (61.6)	
Bilobectomy	1 (0.2)	1 (0.3)	0 (0.0)	
Surgical approach				0.174
Thoracotomy	212 (42.4)	166 (44.3)	46 (36.8)	
Thoracoscopy	288 (57.6)	209 (55.7)	79 (63.2)	
Adjuvant treatment	54 (10.8)	39 (10.4)	15 (12.0)	0.622
Recurrence	29 (5.8)	25 (6.7)	4 (3.2)	0.187
Locoregional	23 (4.6)	20 (5.3)	3 (2.4)	
Distant	4 (0.8)	3 (0.8)	1 (0.8)	
Both	2 (0.4)	2 (0.6)	0 (0.0)	
Mortality	40 (8.0)	32 (8.5)	8 (6.4)	0.569
Pathological findings				
Pathological size, mm	16.0 [10.0, 23.0]	15.0 [10.0, 24.0]	17.0 [12.0, 21.0]	0.593
TNM staging				0.127
IA	418 (83.6)	319 (85.1)	99 (79.2)	
IB	82 (16.4)	56 (14.9)	26 (20.8)	
Minimally invasive adenocarcinoma	78 (15.6)	61 (16.3)	17 (13.6)	
IASLC histological grading				0.012
IASLC grade 1	56 (11.2)	47 (12.5)	9 (7.2)	
IASLC grade 2	288 (57.6)	220 (58.7)	68 (54.4)	
IASLC grade 3	78 (15.6)	47 (12.5)	31 (24.8)	
STAS positive	77 (17.9)	42 (13.5)	35 (29.7)	<0.001
Lymphovascular invasion	36 (7.2)	26 (6.9)	10 (8.0)	0.691
Perineural invasion	2 (0.4)	1 (0.3)	1 (0.8)	0.438
Visceral pleural invasion	49 (9.8)	30 (8.0)	19 (15.2)	0.024

Abbreviations: IASLC, International Association for the Study of Lung Cancer; STAS, spread through air space.

patients with IASLC grade 3 (Table S2). Thus, the predictive ability of the MOSS score in the testing set was promising, with an AUC of 0.820 (95% CI: 0.764–0.875; Figure 3).

DISCUSSION

This study analyzed the clinical and histopathological outcomes of resected pulmonary adenocarcinoma and applied the results to identify patients who have a higher risk of having aggressive tumor histology based on preoperative clinical and radiological factors. To the best of our knowledge, no previous study has developed such a novel scoring system based on preoperative characteristics and presented a simplified approach for detecting early-stage lung cancer patients with a more aggressive histological grading. This score could be used to plan the extent of lung parenchymal resection and meticulous lymph node dissection for patients who have a high probability of having IASLC grade 3 adenocarcinoma.

The impact of male sex on high-grade histology requires consideration. Cha et al. presented male sex as a risk factor for the presence of a solid component based on the analysis of 511 patients with lung adenocarcinoma <3 cm.[12] Moreover, male sex was significant only in univariable analysis in a study of 781 patients in Japan.[11] From a Swedish national cohort study that analyzed 6456 patients, the survival benefit of female sex was observed in adenocarcinoma and stage I subgroup patients. Other studies on sex-based differences in the timing of recurrence for NSCLC also revealed an earlier peak in recurrence among male patients who had undergone surgery.[14] Although there could be other potential confounding factors, such as physical activity, social support, and diet, between males and females, sex-based differences in histological patterns require further investigation.

TABLE 3 Predictive factor analysis for IASLC grade 3 adenocarcinoma.

	Univariate analysis		Multivariate analysis	
Factors	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Age over 65	1.60 (0.87–2.96)	0.130		
Male (ref. female)	3.19 (1.68–6.07)	<0.001	3.77 (1.34–10.7)	0.012
BMI over 25	2.46 (1.30–4.64)	0.005	2.63 (1.18–5.87)	0.018
Hypertension	1.62 (0.88–3.00)	0.120		
Diabetes mellitus	1.21 (0.57–2.56)	0.620		
Cardiovascular diseases	1.77 (0.69–4.58)	0.240		
Smoking history [ref. never smoker]	2.92 (1.55–5.50)	0.001	0.71 (0.25–2.03)	0.521
FEV1/FVC ratio over 70%	0.80 (0.40–1.57)	0.510		
Carcinoembryonic antigen	1.01 (0.95–1.08)	0.690		
Hemoglobin (g/dL)	0.99 (0.92–1.07)	0.820		
Right lesion [ref. left]	0.58 (0.31–1.08)	0.085	0.64 (0.29–1.45)	0.290
Upper lesion [ref. lower]	0.68 (0.37–1.26)	0.220		
Longest diameter on CT over 10 mm	9.87 (2.35–41.5)	0.002	6.04 (0.72–50.5)	0.097
Radiological characteristics[a]				
Part solid	Ref			
Pure ground-glass opacity	0.48 (0.06–4.06)	0.500		
Pure solid	20.4 (8.27–50.4)	<0.001	14.5 (4.90–42.9)	<0.001
^{18}F-FDG uptake on PET/CT[b]				
No uptake	ref			
Mild uptake [0 < SUVmax <2.5]	3.01 (0.88–10.4)	0.080		
High uptake [SUVmax ≥2.5]	10.9 (3.71–32.2)	<0.001	1.29 (0.51–3.27)	0.590

Abbreviations: BMI, body-mass index; CT, computed tomography; ^{18}F-FDG, 18F-fluorodeoxyglucose FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IASLC, International Association for the Study of Lung Cancer; PET, positron emission tomography; SUVmax, maximum standardized uptake value.

[a]Consolidation/tumor ratio (CTR) was used for classification: part solid, 0 < CTR <1; pure ground-glass opacity (GGO), CTR = 0; pure solid, CTR = 1.

[b]Maximum standardized uptake value (SUV_{max}) was used for classification: Moderate, 0 < SUV_{max} <2.5; High, SUV_{max} ≥2.5.

The impact of high BMI (>25.0 kg/m^2) on high-grade histopathology should be carefully interpreted. The adverse impact of obesity on tumor progression or aggressive tumor features have previously been observed in colorectal and prostate cancer.[15,16] However, lung cancer has shown different outcomes among obese patients. The "obesity paradox in lung cancer" suggests that obesity leads to cancer development; however, after diagnosis, obese lung cancer patients tend to respond better to treatment.[17–20] The role of confounding factors in this phenomenon and the plausibility of BMI as a modality to measure adiposity have been debated. Even though patients have high BMI, the presence of sarcopenia could lead to a poor clinical outcome.[20] In the analysis of 20 937 patients in the International Lung Cancer consortium, the impact of BMI on clinical outcome was not observed in Asian patients.[21] In terms of the reliability of BMI as an assessment of adiposity, Barbi et al. reported the visceral fat index as an alternative to BMI and described the relationship between the progression of lung cancer and visceral obesity.[22] Given the lack of sufficient evidence to explain the relationship between high BMI and high-grade adenocarcinoma, further studies are necessary to interpret the results of our study on the MOSS score.

Solid lesions on CT scans have clear prognostic value in terms of prognosis. In a radiomics study for differentiation of predominant subtypes, a solid appearance was included as a solid-predominant adenocarcinoma.[23,24] A previous study also suggested solid lesion as a predictive factor for IASLC grade 3 adenocarcinoma.[11] As pulmonary lesions with ground glass opacity are known for having lepidic predominant pattern, this interpretation of radiological imaging corresponds to the current knowledge of radiology in lung cancer.

Our study revealed that four preoperative factors were related to poor histological grading. Each factor included in the MOSS scoring was in agreement with previous studies on predictive factors for high-grade adenocarcinoma. Fujikawa et al. reported that smoking, solid lesions on CT images, younger age, and SUV_{max} on PET/CT were related to IASLC grade 3.[11] In our study, a high SUV_{max} was significant in univariate analysis, but its effect was not significant in multivariate analysis. Since our study included a higher number of early cancer stage and younger patients than the other studies, the impact of PET/CT could be lessened. The application of each significant factor could have diverse impacts, depending on the characteristics of the patients investigated.

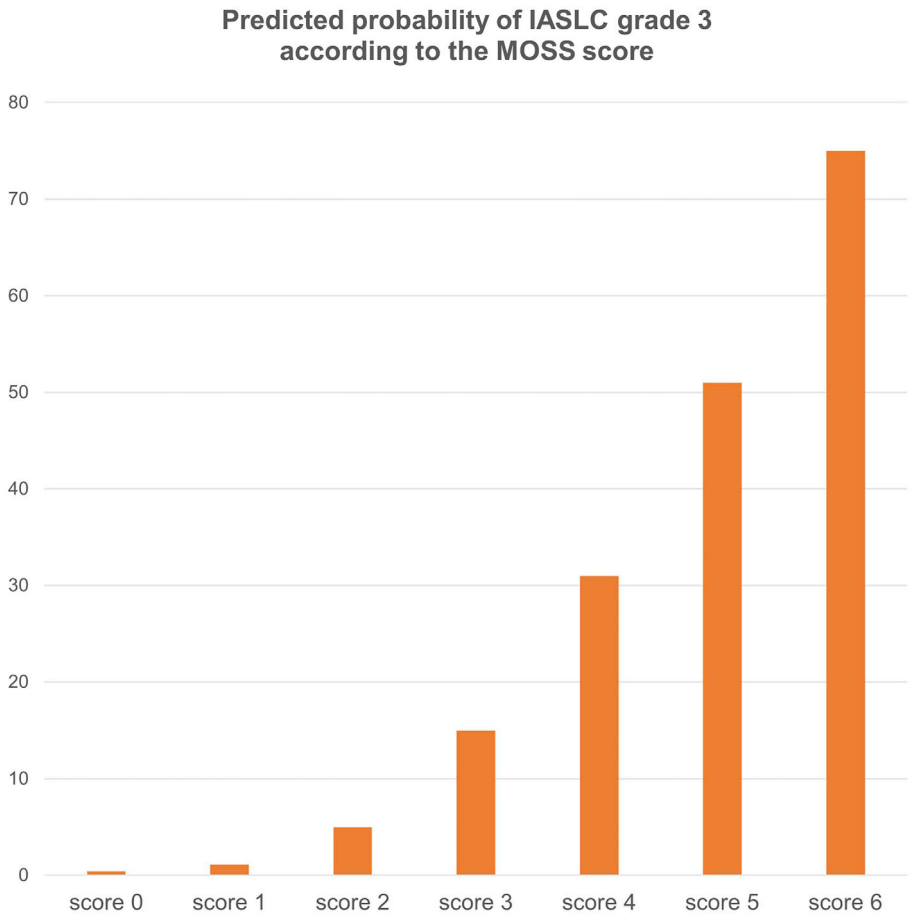

FIGURE 2 Probability of IASLC grade 3 according to the MOSS score. IASLC, International Association of the Study for Lung Cancer.

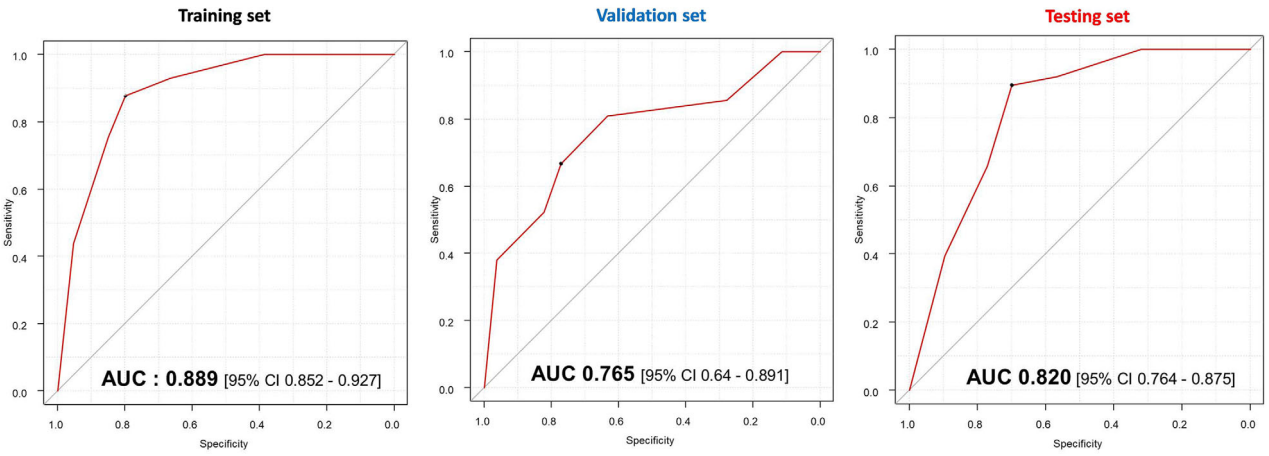

FIGURE 3 Receiver operating characteristic (ROC) curve and area under the curve (AUC) of the MOSS score for each dataset.

In our practice, we applied this scoring system as a supplemental tool with intraoperative biopsy. If frozen biopsy revealed minimally invasive adenocarcinoma or adenocarcinoma in situ, sublobar resection and limited mediastinal lymph node dissection were preferred. In cases with invasive adenocarcinoma, MOSS score 4 or more was considered aggressive histological patterns; lesions should be pure solid without GGO to have scored 4 or above. For these cases, we expanded the extent of mediastinal lymph node dissection to increase the detection rate of N2 skip metastasis. Prospective application of this score needs to be evaluated for a longer period. However, we believe that this type of score could lower procedure bias at the surgeons' discretion.

Our study had some limitations. First, although patients were diagnosed with high-grade adenocarcinoma, their OS can depend on several other factors, such as adjuvant

treatment, functional capacity, and molecular mutations. The survival benefit of adjuvant chemoradiotherapy was influenced differently by histological patterns in a previous study, revealing improved outcomes for patients with solid-predominant tumors.[25] Therefore, the diagnosis of IASLC grade 3 should not be solely interpreted as indicating a poor outcome. Second, this scoring system has not been validated in different institutions with diverse patient populations. Therefore, the predictive ability of the MOSS score needs to be tested in other clinical environments. However, as its prognostic value was approved in the clinical stage I population, this score may introduce a new approach for patient risk stratification.

In conclusion, in this study, we analyzed preoperative characteristics of early-stage pulmonary adenocarcinomas and suggested a new scoring system to predict IASLC grade 3 adenocarcinomas. The MOSS score, which combines male sex, overweight, size >10 mm, and solid lesions, could be used to assess early-stage NSCLC by differentiating high-risk patients, thereby facilitating prompt management and treatment. The scoring system can be improved with the accrual of more evidence and research on early-stage NSCLC.

AUTHOR CONTRIBUTIONS

WW: Conceptualization, methodology, validation, data curation, formal analysis, investigation, software, writing–original draft, writing—review and editing.

YJC: Methodology, validation, data Curation, writing—review and editing.

CHP: Methodology, validation, data curation, writing—review and editing.

DHM: Conceptualization, methodology, validation, data curation, supervision, writing—review and editing. SL: Conceptualization, methodology, validation, supervision, project administration, writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Wongi Woo https://orcid.org/0000-0002-0053-4470
Sungsoo Lee https://orcid.org/0000-0001-8998-9510

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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