

Efficacy of a combined tool for stage I non-small cell lung cancer against lymph node metastasis

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Abstract. In patients with clinical stage I non-small cell lung cancer (NSCLC), the prediction of occult lymph node metastasis (LNM) based on a combination of morphology using high-resolution computed tomography (HRCT) and metabolism using positron emission tomography (PET)-CT is unknown. The present study evaluated the use of predictive radiological tools, chest CT and PET-CT, for occult LNM in patients with clinical stage I NSCLC. The records of patients who underwent lobectomy between July 2014 and November 2021 were retrospectively reviewed. The differences in clinicopathological parameters, including CT and PET, between the LNM and non-LNM groups were assessed. Pure solid tumor was defined as a consolidation-to-tumor ratio of 1. The optimal cut-off value for predictive radiological tools for LNM was assessed according to the area under the receiver operating characteristic (ROC) curve. The present study included 288 patients, of whom 39 (13.5%) had LNM; of these 38 (97.4%) were pure solid type. Larger consolidation size (CS), higher maximal standardized uptake (SUVmax) value and histological type were statistically associated with LNM (all $P < 0.05$). The optimal cutoff values of CS and SUVmax for predicting LNM were 19 mm and 5.5 respectively, as assessed using the area under the ROC curve. The combination of CS ≥ 19 mm and SUVmax ≥ 5.5 demonstrated a markedly higher odds ratio (9.184; 95% CI, 4.345-19.407) than each parameter

individually. The minimum values of CS and SUVmax associated with LNM were 10 mm and 0.8 respectively. Pure solid formation and CS as morphology and SUVmax as metabolism were useful tools that complemented each other in predicting LNM. The combined method of evaluating SUVmax and CS may identify eligibility for LN dissection. However, considering the minimum values of CS and SUVmax in LNM, it cannot affirm the omission of LN dissection for cases that do not meet the combined criteria using HRCT and PET-CT.

Introduction

Predicting oncological behavior is important when deciding between a surgical plan, aggressive surveillance and aggressive adjuvant or neoadjuvant therapy (1). The 8th edition of the tumor-node-metastasis (TNM) classification for non-small cell lung cancer (NSCLC) is used worldwide (2). Computed tomography (CT) is used to define the clinical T category of NSCLC (2). Numerous radiological observations using CT have been reported to predict the prognosis of NSCLC, including whole tumor size (WTS), consolidation size (CS), consolidation-to-tumor ratio (CTR), tumor disappearance ratio (TDR), tumor diameter in the mediastinal window (MD) and presence of ground-glass opacity (GGO). Parameters were defined as follows. WTS, whole tumor size on lung window setting; CS, consolidation size on lung window setting, MD, diameter on mediastinal window setting; CTR, CS/WTS; and TDR (%), $100 \times (1 - (MD/WTS))$. In the 8th edition of the TNM classification, clinical T category is assigned based on CS assessed using high resolution CT (2). In 2019, Kim *et al* (3) reported that CTR and TDR are not independently associated with long-term prognosis of NSCLC compared with clinical T category using CS. The presence of GGO on CT has been reported to indicate good prognosis in both clinical and pathological T1N0-staged NSCLC (4-6). However, the best prognostic radiological tools for solid nodules without GGO in the early stage remain unknown.

A previous randomized clinical trial demonstrated that positron emission tomography-CT (PET-CT) contributes to the preoperative staging of NSCLC and decreases the number of futile surgeries (7). The National Comprehensive Cancer Network and Japanese Lung Cancer Society Guideline recommend the use of ^{18}F -fluorodeoxyglucose (FDG)-PET-CT determine the presence of distant metastases requiring surveillance (1,8). Previous studies have reported the usefulness of maximal standardized uptake (SUVmax) value using PET-CT

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Abbreviations: AUC, area under the curve; CS, consolidation size; CT, computed tomography; CTR, consolidation-to-tumor ratio; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; FDG, ^{18}F -fluorodeoxyglucose; GGO, ground-glass opacity; LNM, lymph node metastasis; MIA, minimally invasive adenocarcinoma; NSCLC, non-small cell lung cancer; OR, odds ratio; PET, positron emission tomography; ROC, receiver operating characteristic; TDR, tumor disappearance ratio; TNM, tumor-node-metastasis; WTS, whole tumor size

Key words: lung cancer, CT, PET, LNM, CTR

(calculated based on the maximum activity of the volume of the dose of FDG injected and patient weight), associated with primary tumors for assessing the risk of occult lymph node metastasis (LNM) using numerous cut-off values (9-11).

Despite previous studies on tumor morphology using high-resolution CT (HRCT) and tumor metabolism using PET-CT have been reported, the success of prediction of LNM based on the combination of morphology and metabolism using these radiological tools is not known to clinicians (4-6,10-12). Therefore, in the present study, predictive radiological tools (chest HRCT and PET-CT) for occult LNM in patients with clinical stage I NSCLC were evaluated.

Materials and methods

Patients. The clinicopathological data of 420 patients who underwent lobectomy for clinical stage I NSCLC at The Jikei University School of Medicine (Tokyo, Japan) between July 2014 and November 2021 were retrospectively reviewed. All enrolled patients were evaluated using tumor markers, chest and abdominal CT, brain magnetic resonance imaging or CT and PET-CT before surgery. The present study was performed in accordance with The Declaration of Helsinki. The data were retrospectively collected, registered in a database and approved by the Review Board of The Jikei University School of Medicine [approval number: 30-359(9380)].

Data collection. During the study period, 514 patients underwent lobectomy at The Jikei University School of Medicine for primary lung cancer, of whom 288 patients met the inclusion criteria (Fig. 1). The median age of the patients was 70 years (range, 31-87 years) and there were 189 males and 99 females. The following patient characteristics were collected: Age, sex, smoking index, body mass index, Charlson Comorbidity Index score calculated based on comorbid conditions and preoperative spirometry test, including vital capacity and forced vital capacity. *Carcinoembryonic antigen* and cytokeratin 19 fragment were evaluated as tumor markers in preoperative blood tests within 2 months before surgery. WTS and CS in the lung window setting were observed on CT. CTR was calculated as CS/WTS and tumors were classified as a pure solid tumor (CTR=1), part solid tumor (CTR<1) or pure GGO (CTR=0). For convenience in classifying tumors according to CTR, the definition of pure solid tumors included tumors with minor GGO components outside of the CTR measurement site. All patients underwent PET-CT based on glycemic control. SUVmax was evaluated using PET-CT. A surgical plan for each patient was decided by preoperative conference. Mediastinal lymph node (LN) dissection was evaluated in terms of surgical parameters [nodal dissection (ND) level 1/2a-1/2a-2]; level of mediastinal LN dissection was determined at a preoperative conference (13). Patients with multiple comorbidities were omitted from mediastinal LN dissection. Mediastinal LN sampling was included in LN dissection status NDI. The total number of excised LNs was counted. Pathological parameters included histological type (adenocarcinoma, squamous cell carcinoma or other), pathological whole size, invasive size, lympho-vascular and pleural invasion and LNM. Histological assessment was performed according to the 8th edition of the TNM classification (2). The involvement of LN was assessed as a short

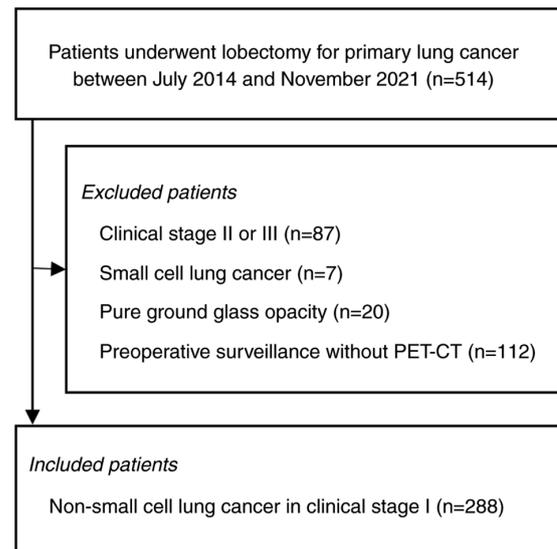


Figure 1. Flowchart of patient inclusion and exclusion. PET-CT, positron emission tomography-computed tomography.

diameter (>10 mm on CT), focally increased FDG uptake compared with normal background uptake or SUVmax >2.5 on PET. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was performed for suspected LNM during preoperative surveillance.

The exclusion criteria were as follows: Patients with clinical stage II or III, SCLC, benign tumors, pure GGO on CT, preoperative surveillance without PET-CT and incomplete data.

Statistical analysis. Statistical analysis was performed using SPSS version 21.0 software (IBM Corp.). P<0.05 was considered to indicate a statistically significant difference. Data are presented as median and interquartile range or mean \pm standard deviation. Quantitative continuous variables were compared using Student's t-test for the mean and Mann-Whitney U test for the median. Fisher's exact and χ^2 test were used to compare categorical variables. Parameters with P<0.05 in the univariate analysis were selected for inclusion in multivariate logistic regression analysis.

Multivariable parameters between LNM and non-LNM groups in the whole cohort were compared. The optimal cut-off value for predictive radiological tools for LNM was assessed according to the area under the receiver operating characteristic (ROC) curve.

Results

Patient characteristics. There were 175 patients (60.8%) with pure solid tumors. In total, 39 (13.5%) patients were diagnosed with pathological LNM, of which 38 (97.4%) were pure solid tumors. EBUS-TBNA was performed on one patient with combined background pulmonary fibrosis and emphysema. The lower paratracheal LN with SUVmax of 5.7 was negative on EBUS and positive on postoperative pathology with false negative.

Comparison of multivariable parameters between LNM and non-LNM groups. Larger WTS (P<0.05) and CS (P<0.001),

Table I. Comparison of pathological patients with non-LNM and LNM clinical stage I non-small cell lung cancer.

Clinicopathological characteristic	Non-LNM (n=249)	LNM (n=39)	P-value
Age, years, median (IQR)	70.0 (63.0-75.0)	67.0 (62.0-74.0)	0.440 ^a
Male, n (%)	164.0 (65.9)	25 (64.1)	0.727 ^b
Smoking index, mean ± SD (range)	653.8±732.9 (0-6000)	509.2±536.0 (0-1760)	0.238 ^c
BMI, median (IQR)	22.4 (19.8-24.3)	22.6 (19.5-24.4)	0.624 ^a
CCI, mean ± SD (range)	1.1±1.2 (0.0-7.0)	0.8±1.2 (0.0-4.0)	0.167 ^c
Spirometry			
VC, ml, median (IQR)	3210.0 (2740.0-3820.0)	3220.0 (2629.0-3770.0)	0.766 ^a
FVC, ml, median (IQR)	3230.0 (2695.0-3770.0)	3475.0 (3060.0-4105.0)	0.121 ^a
Findings on CT			
Whole tumor size, mm, median (IQR)	22.0 (15.0-28.0)	25.0 (19.0-35.0)	0.045 ^a
Consolidation size, mm, median (IQR)	15.0 (11.0-23.0)	25.0 (19.0-35.0)	<0.001 ^a
Pure solid tumor, n (%)	137.0 (55.0)	38 (97.4)	<0.001 ^b
SUVmax, mean ± SD (range)	5.5±5.0 (0.6-42.1)	9.4±6.5 (0.8-25.0)	<0.001 ^c
CEA, mean ± SD (range)	6.4±13.9 (0.9-208.0)	7.5±6.9 (0.8-40.5)	0.647 ^c
CYFRA, mean ± SD (range)	2.7±3.2 (0.7-39.4)	2.2±1.6 (0.9-8.4)	0.444 ^c
Lymph node dissection ND1/ND2a-1/ND2a-2 (%)	67.0/181.0/1 (26.9/72.7/0.4)	11.0/28.0/0.0 (28.2/71.8/0.0)	0.868 ^d
Total number of excised lymph nodes, mean ± SD (range)	13.4±7.3 (1.0-41.0)	14.4±8.9 (3.0-36.0)	0.427 ^c
AD/SQ/other, n (%)	182/55/12 (73.1/22.1/4.8)	28/4/7 (71.8/10.3/17.9)	0.003 ^b
Pathological whole size, mm, median (IQR)	22.0 (15.0-30.0)	25.0 (20.0-37.0)	0.046 ^a
Pathological invasive size, mm, median (IQR)	14.0 (7.0-22.0)	24.0 (17.0-37.0)	<0.001 ^a
Lympho-vascular invasion, n (%)	73.0 (29.3)	34.0 (87.2)	<0.001 ^b
Pleural invasion, n (%)	52.0 (20.9)	18.0 (46.2)	<0.001 ^b

^aMann-Whitney test; ^b χ^2 test; ^cStudent's t-test; ^dFisher's exact test. LNM, lymph node metastasis; IQR, interquartile range, BMI, body mass index; CCI, Charlson comorbidity index; VC, vital capacity; FVC, forced vital capacity; CT, computed tomography; SUVmax, maximal standardized uptake; CEA, *carcinoembryonic antigen*; CYFRA, cytokeratin 19 fragment; ND, nodal dissection; AD, adenocarcinoma; SQ, squamous cell carcinoma; SD, standard deviation.

pure solid tumor ($P<0.05$), higher SUVmax ($P<0.001$), histological type ($P<0.05$), pathological whole ($P<0.05$) and invasive size ($P<0.001$) and lympho-vascular ($P<0.001$) and pleural invasion ($P<0.001$) were significantly associated with LNM (Table I). According to the respective minimum values of CS and SUVmax, CS of 10 mm and SUVmax of 0.8 were associated with LNM.

Cut-off values of SUVmax and CS associated with LNM.

Analysis of the area under the ROC curve demonstrated that the optimal cutoff value of SUVmax for predicting LNM was 5.5 [area under the curve (AUC), 0.720; sensitivity, 71.8%; specificity, 62.2%; 95% confidence interval (CI), 0.639-0.801; $P<0.001$; Fig. 2]. The optimal cut-off value of CS for predicting LNM was 18.5 mm (AUC, 0.752; sensitivity, 79.5%; specificity, 62.2%; 95% CI, 0.673-0.831; $P<0.001$; Fig. 3). These results indicated that SUVmax and CS were useful predictive radiological tools for LNM.

Odds ratios (ORs) for LNM according to radiological parameters. ORs for LNM according to radiological parameters, including CS ≥ 19 mm, SUVmax ≥ 5.5 , CS ≥ 19 mm + SUVmax ≥ 5.5 and pure solid tumor were calculated. CS and SUVmax are similar in terms of quantitative radiation scale.

These tools were evaluated for their ORs for LNM when used alone and in combination, respectively. OR of CS ≥ 19 mm was 6.390 (95% CI, 2.819-14.484; $P<0.001$). OR of SUVmax ≥ 5.5 was 4.740 (95% CI, 2.251-9.979; $P<0.001$). CS ≥ 19 mm + SUVmax ≥ 5.5 demonstrated an OR of 9.184 (95% CI, 4.345-19.407; $P<0.001$). The pure solid tumor OR was 31.066 (95% CI, 4.199-229.87; $P<0.001$; Table II). Scatter diagrams of LNM for both CS and SUVmax (Fig. 4) demonstrated that CS ≥ 19 mm + SUVmax ≥ 5.5 indicated high risk for LNM.

Discussion

In NSCLC, primary tumor with a GGO component has a better prognosis than a solitary tumor (4-6). Hattori *et al* (14) reported that the presence or absence of GGO should be considered an essential parameter in clinical T classification. Suzuki *et al* (15) demonstrated that sufficient local control and recurrence-free survival (RFS) can be achieved by sub-lobar resection with adequate surgical margin for lung cancer with a maximum tumor diameter ≤ 2.0 cm and CTR ≤ 0.25 based on thin-section CT that has been clinically determined as N0. In patients with sub-centimeter NSCLC with high SUVmax, Hattori *et al* (16) reported that lobectomy is associated with better 3-year RFS than sub-lobar resection (88.3 vs. 50.0%,

Table II. Odds ratios for lymph node metastasis according to radiological parameters.

Parameter	Odds ratio	95% confidence interval	P-value
CS \geq 19 mm	6.390	2.819-14.484	<0.001
SUVmax \geq 5.5	4.740	2.251-9.979	<0.001
CS \geq 19 mm + SUVmax \geq 5.5	9.184	4.345-19.407	<0.001
Pure solid tumor	31.066	4.199-229.870	<0.001

CS, consolidation size; SUVmax, maximal standardized uptake.

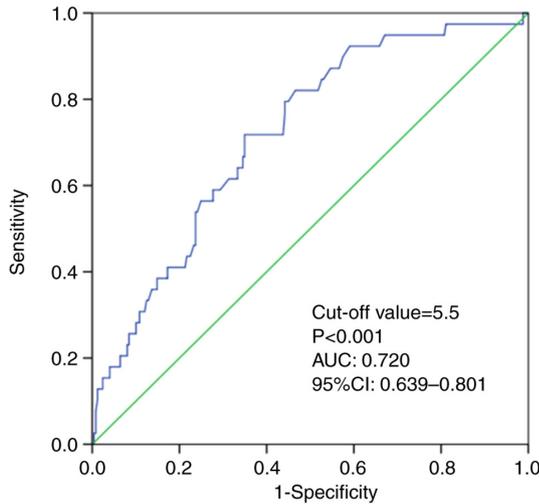


Figure 2. Receiver operating characteristic curve of SUVmax for predicting lymph node metastasis. SUVmax, maximal standardized uptake; AUC, area under the curve; CI, confidence interval.

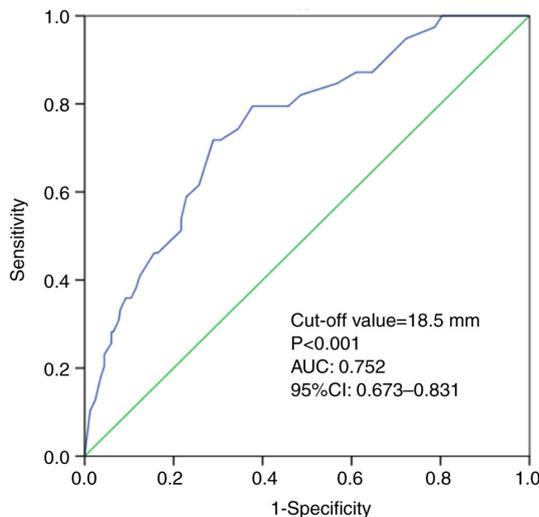


Figure 3. Receiver operating characteristic curve of consolidation size assessed using computed tomography imaging for predicting lymph node metastasis. AUC, area under the curve; CI, confidence interval.

P=0.0453); for patients with pure-solid sub-centimeter NSCLC and high SUVmax, major lung resection with LN dissection is required for radical locoregional management to prevent recurrence. In the present study, the predictive radiological

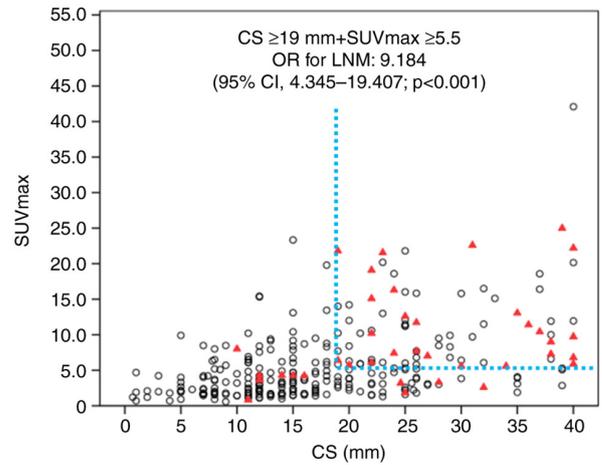


Figure 4. CS + SUVmax is a predictor of LNM. CS \geq 19 mm + SUVmax \geq 5.5 predicts LNM. Triangles represent LNM group. Circles represent non-LNM group. LNM, lymph-node-metastasis; SUVmax, maximal standardized uptake value; CS, consolidation size; OR, odds ratio; CI, confidence interval.

tools chest CT and PET-CT for occult LNM classification for clinical stage I NSCLC were evaluated. Various radiological findings using CT have been reported as predicting prognosis of NSCLC, including WTS, CS, CTR, TDR, MD and presence of GGO (12). Our previous review reported that numerous studies have demonstrated that CS is the most useful CT morphology method for predicting malignant behavior regarding NSCLC (12,17-23). Therefore, in the present study, CS was used for morphological assessment using CT.

In the present study, larger CS, pure solid tumor and higher SUVmax demonstrated significant association with LNM (all P<0.05). In total, 39 (13.5%) patients were diagnosed with pathological LNM. Lesions were pure solid type for 38 (97.4%) of these patients. For convenience, the definition of pure solid tumors in the present study included tumors with minor GGO components outside of the CTR measurement site. Numerous authors have suggested that part-solid tumors should be considered a clinical subtype with better prognosis for both clinical and pathological T1N0-staged lung adenocarcinomas (4-6). In both clinical and pathological T1N0-staged NSCLC, solid tumors with no GGO and larger CS are associated with longer disease-free survival (21-23). In the present study, SUVmax and CS were shown to be useful in predicting occult LNM. Optimal cut-off values of SUVmax and CS for predicting LNM were 5.5 and 18.5 mm, respectively. CS \geq 19 mm + SUVmax \geq 5.5 demonstrated a markedly

higher OR than these parameters separately (OR, 9.184; 95% CI, 4.345-19.407). The scatter diagrams of SUVmax and CS demonstrated that CS ≥ 19 mm + SUVmax ≥ 5.5 indicated high risk for LNM; this may assist in surgical planning. Pure solid type was a marked risk factor for LNM (OR, 31.066; 95% CI, 4.199-229.87). Considering all the results, it was determined that pure solid type and CS as morphological factors and SUVmax as a metabolic factor were useful tools that complemented each other in predicting LNM. The combined method of evaluating SUVmax and CS may support determination of eligibility for LN dissection.

Minimally invasive adenocarcinoma (MIA) has good prognosis owing to the absence of lymphatic, vascular or pleural invasion or necrosis (24). Several radiological tools have been reported for the identification of lympho-vascular invasion and LNM using CT (12,25,26). Hayashi *et al* (25) reported that solid component size (tumor diameter in the MD >5 mm or CS >8 mm) predicts LNM and local invasiveness in T1 lung adenocarcinoma. In the present study, CS of 10 mm was the minimum value for LNM. Sakakura *et al* (26) reported that MD ≤ 2 mm predicts MIA with a specificity of 94.5%. Previously, CS ≤ 5 mm was defined as cT1mi category in the 8th TNM classification (2).

PET-CT is an imaging method that predicts tumor activity by measuring tumor metabolism. However clinicians cannot overlook differences in SUVmax when using PET-CT because SUVmax varies due to different types of PET-CT scanners in each facility (27). SUVmax of the primary tumor is useful for predicting occult LNM in patients with lung cancer (11,28,29). Park *et al* (28) suggested that SUVmax >7.3 in primary tumor independently predicts LNM in clinical stage IA NSCLC. Furthermore, Kaseda *et al* (11) reported that the optimal cut-off value for tumor SUVmax to predict LNM using the ROC curve is 3.0 in clinical stage I NSCLC. Nambu *et al* (29) reported that the minimum SUVmax for tumors in an LNM group is 2.5. Compared with these effective values of SUVmax, our study showed that SUVmax ≥ 5.5 was the cutoff value for occult LNM, which was within the range of previously reported values (11,28,29). However, in the present study, the minimum values of CS and SUVmax associated with LNM were 10 mm and 0.8 respectively. Therefore, the results of the present study do not confirm omission of LN dissection for patients who do not meet the cut-off values for CS and SUVmax. By eliminating the differences in SUV measurement between centers, it may be possible to develop surgical strategies based on PET and CT findings for use in clinical practice worldwide.

The present study had certain limitations. This retrospective observational study was performed in only a single facility. Furthermore, other CT parameters, including pleural indentation, lobule and notch are important in predicting behavior of malignancy; however, these radiological tools were not considered. Depending on patient comorbidities, mediastinal LN dissection was omitted or limited to mediastinal LN sampling; this lack of uniformity in level of mediastinal LN dissection may have resulted in missed occult LNM and affected the analysis. Further studies are needed to evaluate LNM with more accurate pathological study.

Pure solid formation and CS morphology and SUVmax as a metabolic aspect are useful tools that complement each other in predicting LNM. The combined method of evaluating

SUVmax and CS identifies eligibility for LN dissection. However, considering the minimum values of CS and SUVmax in LNM, it cannot affirm the omission of LN dissection for cases that do not meet the combined criteria using HRCT and PET-CT.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TN conceived the study, designed and performed the experiments, analyzed data and wrote the manuscript. MY designed and performed the experiments and edited the manuscript. TO performed the experiments, supervised the study and edited the manuscript. TN and MY confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was performed according to the guidelines of the Declaration of Helsinki and approved by the Review Board of Jikei University School of Medicine [approval no. 30-359(9380)].

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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