

Resection of calcified lymph nodes confers clinical benefit in patients with non-small cell lung cancer

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Abstract. The aim of the present study was to compare the metastatic ratio between calcified lymph node stations (CLNS) and non-CLNS (NCLNS) and to explore the impact of CLNS on surgical outcomes. Consecutive patients with non-small cell lung cancer (NSCLC) scheduled to receive surgical treatment between June and December 2020 were included in the present study. Their clinical and radiological data were prospectively collected and analyzed. A total of 91 patients with NCLNS and 64 patients with CLNS were enrolled in the present study. Out of the 91 patients, 38 (24.516%) patients had 61/343 (17.784%) lymph node stations (LNS) that were metastasized. On a per-patient basis, the differences in the LNS metastatic ratio were not significant between the CLNS with NCLNS groups. However, on a per-nodal station basis, all differences in the LNS metastatic ratio between the groups were significant not only in the all-LNS group ($P=0.004$), but also in the LNS group which in patients with solely CLNS or NCLNS ($P=0.009$) and in the patients with CLNS ($P=0.010$). Pathology, T stage and calcification were independent predictive factors for LNS metastasis ($P=0.002$, $P=0.021$ and $P=0.044$, respectively). More patients with CLNS than patients with NCLNS received thoracotomy or conversion from video-assisted thoracoscopic surgery to thoracotomy ($P=0.006$). The operating time and blood loss were significantly higher in patients with CLNS than in those without ($P<0.001$ and $P<0.001$, respectively). Although CLNS are a risk reduction factor for metastasis and their dissection is time- and blood-consuming in patients with NSCLC, their thorough removal is advisable, since metastases were identified in ~15% of patients and 9% of CLNS.

Introduction

Preoperative evaluation of mediastinal lymph nodes (LNs) in patients with lung cancer is essential for determining optimal treatment strategies in the management of primary lung cancer. On the one hand, the status of mediastinal LNs metastasis can not only affects the formulation of perioperative diagnosis and treatment strategies (1-3), but also affects the survival time of patients after surgery (4-6). Therefore, the current National Comprehensive Cancer Network guidelines for non-small cell lung cancer (NSCLC) suggests that N1 (ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes) and N2 (ipsilateral mediastinal and/or subcarinal lymph node(s)) node resection and mapping should be a routine component of lung cancer resections with a minimum of three N2 stations sampled or complete lymph node dissection (7). On the other hand, mediastinal calcified LNs (CLNs) is generally considered to be benign and are often caused by granulomatous disease, sarcoidosis, silicosis and *Pneumocystis jirovecii* infection; however, they can also be due to metastases from ovarian cancer, colonic adenocarcinoma, osteosarcoma or papillary thyroid carcinoma (8,9). Previous case reports (10-12) and a small sample study (13) have confirmed that primary lung cancer could metastasize to CLNs (14/72 patients; 19.4%). In addition, several previous studies have confirmed that CLN was an important predictive factor of conversion from a video-assisted thoracoscopic surgery (VATS) to thoracotomy (conversion rate, 29.41-40.6%), which was due to adhesion between CLN stations (CLNS) and hilar structures, and the subsequent difficulty of their dissection (14-17). However, the clinicopathological characteristics of CLNS in the preoperative computed tomography (CT) scans of patients with NSCLC have not been fully investigated.

Therefore, in the present study, the difference in metastatic ratio between CLNS and non-CLNS (NCLNS) was investigated based on preoperative thin-slice CT scans of patients with NSCLC who underwent uniportal VATS lobectomy and systemic mediastinal nodal dissection. Furthermore, the impact of CLNS on surgical outcomes was explored.

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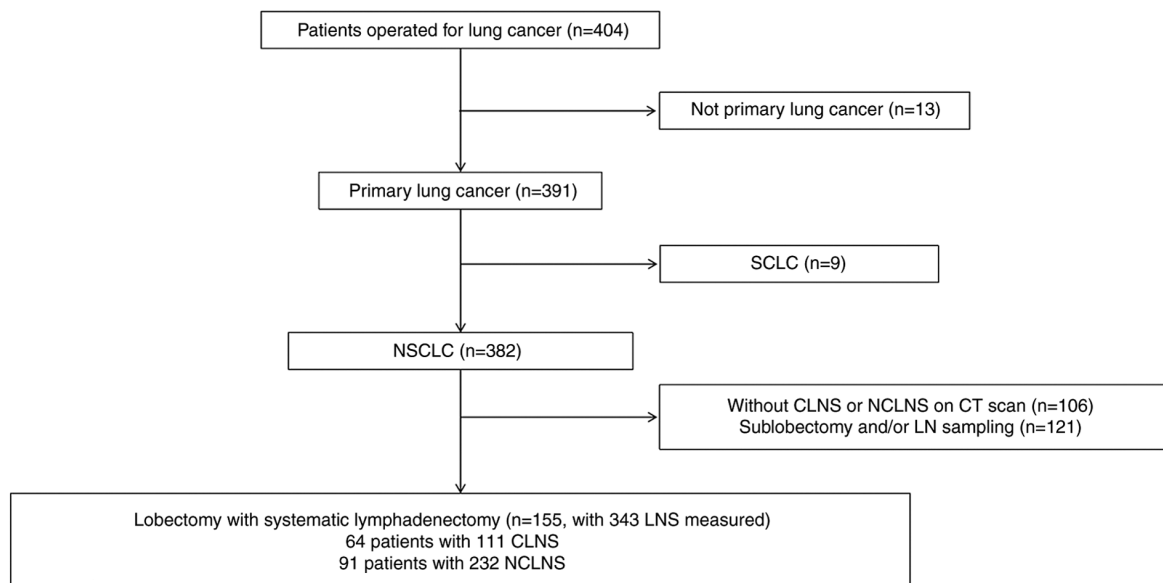


Figure 1. Flowchart of patient selection. CLNS, calcified lymph node station; LN, lymph node; LNS, lymph node stations; NCLNS, non-calcified lymph node station; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

Materials and methods

Clinical data collection. Following approval by the Ethics Committee of The Affiliated Hospital of Guizhou Medical University (approval no. 2020-244), consecutive patients with NSCLC scheduled to receive surgical treatment between June and December 2020 at The Affiliated Cancer Hospital of Guizhou Medical University were included in this study. Fig. 1 includes a flowchart describing patient selection. The clinical and radiological data of patients were prospectively collected and included sex, age, surgical lobes, number of LNS removed, duration of surgery, blood loss, status of LNS on CT scan, tumor specimen size and pathology, as well as T, N and M based on the International Association for the Study of Lung Cancer TNM classification (18). Medical record review was performed in accordance with the institutional ethics review board guidelines (19).

Determination of LNS status. The preoperative CT scans without contrast were performed on a LightSpeed VCT 64-detector scanner (Cytiva) with subjects holding their breath at end inspiration and using the following parameters: Detector configuration, 64x0.625 mm; pitch, 0.969; tube energy, 120 kVp; tube current, 250 mA; gantry rotation, 0.4 sec (or 100 mAs). The CT scan images were saved in DICOM format. The DICOM data were then loaded onto the syngo.plaza software (version VB10B, Siemens AG) to determine the LNS status. A CLNS was defined as an LNS with calcifications of any size. Calcification was determined by visual identification of contiguous 5- and 1-mm sections on mediastinal window setting thin-slice CT scans (window width, 350 HU; level, 40-60 HU). NCLNS were defined as LNS without calcification and with a minimum diameter of ≥ 10 mm.

Surgical procedure. Patients with a tumor size of >7 cm or CLNS involving the pulmonary artery or vein were scheduled to receive a thoracotomy from the beginning. For other

patients, uniportal VATS lobectomy and systemic mediastinal nodal dissection were selected based on their advantages over thoracotomy, assuming that no intractable technical challenge would arise during the procedure. Uniportal VATS lobectomy and systemic mediastinal nodal dissection were performed as previously described (20). The surgeons decided to switch from VATS to thoracotomy if differentiating layers around the pulmonary vessels or bronchus were deemed to be extremely dangerous, or in the event of uncontrolled bleeding, chest wall invasion or limited pulmonary collapse.

Statistical analysis. All data were manually entered to a excel by the same researcher. Descriptive statistics were used to describe the demographic characteristics. Continuous variables are presented as the mean and standard deviation, and categorical variables as numbers and percentages. When variances were equal, two-sample unpaired t-test with equal variances was used for continuous variables. For unequal variances, two-sample Wilcoxon rank-sum (Mann-Whitney) test was used. χ^2 or Fisher's exact test was used for binary categorical data with results are presented as odds ratios (OR) and 95% confidence interval (CI). Ordered logistic regression (ologit) was used for ordered categorical data with results are presented as coefficient (Coef.) and 95% CI. Statistical analysis was performed using Stata 15.0 (StataCorp LP). All statistical tests were two-sided and $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patients and LNS. A total of 155 patients with NSCLC who received surgery were included in the present study. The clinical characteristics of the included patients are presented in Table I. A total of 111 (32.36%) CLNS were identified in 64 (41.29%) patients and 143 (67.64%) NCLNS in 91 (58.71%) patients. A total of 48 patients with CLNS were found to simultaneously have 89 NCLNS. Of them, 4 patients with

Table I. Differences in clinicopathologic characteristics between patients with CLNS and NCLNS.

Characteristics	NCLNS	CLNS	P-value
Patients, n (%)	91 (58.71)	64 (41.29)	-
LN measured, n	232.00	111.00	-
Age, years (mean ± SD)	58.24±10.68	58.95±8.35	0.72 ^a
Sex, n (%)			0.87 ^b
Female	31 (34.07)	21 (32.81)	
Male	60 (65.93)	43 (67.19)	
Lobes, n (%)			0.54 ^b
Left upper	17 (18.68)	9 (14.06)	
Left lower	21 (23.08)	12 (18.75)	
Right upper	23 (25.27)	18 (28.12)	
Right middle	6 (6.59)	9 (14.06)	
Right lower	24 (26.37)	16 (25.00)	
Pathology, n (%)			0.60 ^b
Squamous cell carcinoma	43 (47.25)	33 (51.56)	
Adenocarcinoma	48 (52.75)	31 (48.44)	
Size, mm (mean ± SD)	39.64±15.50	41.61±17.11	0.74 ^a
T stage, n (%)			0.36 ^c
1b	10 (10.99)	4 (6.25)	
1c	17 (18.68)	14 (21.88)	
2a	27 (29.67)	14 (21.88)	
2b	15 (16.48)	18 (28.12)	
3	20 (21.98)	11 (17.19)	
4	2 (2.20)	3 (4.69)	
N stage, n (%)			0.34 ^b
0	52 (57.14)	44 (68.75)	
1	14 (15.38)	7 (10.94)	
2	25 (27.47)	13 (20.31)	

^aTwo-sample t-test; ^bPearson χ^2 test; ^cFisher's exact test. -, not applicable; CLNS, calcified lymph node station; LN, lymph node; NCLNS, non-calcified lymph node station.

Table II. Comparison of metastatic ratio of patients and LNS between the CLNS and NCLNS groups.

Characteristics	Group	Metastasis, (no. of patients or nodes)	Without metastasis (no. of patients or nodes)	Total (no. of patients or nodes)	Metastatic ratio, %	P-value
All patients	C	13	51	64	20.313	0.308 ^a
	N	25	66	91	27.473	
Patients with solely C or N metastasis	C	9	51	60	15.000	0.073 ^a
	N	25	66	91	27.473	
All LNS	C	10	101	111	9.009	0.004 ^b
	N	51	181	232	21.983	
LNS in patients with solely C or N metastasis	C	10	101	111	9.009	0.009 ^b
	N	31	112	143	21.678	
LNS in patients with CLNS	C	10	101	111	9.009	0.010 ^b
	N	20	69	89	22.472	

^aPearson χ^2 test; ^bFisher's exact. C, calcified; CLNS, calcified lymph node station; LNS, lymph node stations; N, non-calcified; NCLNS, non-calcified lymph node station.

Table III. Effects of clinicopathological characteristics on lymph node stations metastasis in patients with calcified lymph node stations or non-calcified lymph node stations.

Characteristics	Single-factor logistic			Multi-factor logistic			Single-factor ologit			Multi-factor ologit		
	OR	95% CI	P-value	OR	95% CI	P-value	Coef.	95% CI	P-value	Coef.	95% CI	P-value
Age	0.982	0.945-1.021	0.358	0.979	0.939-1.021	0.327	-0.017	-0.055-2.486	0.377	-0.021	-0.060-0.019	0.313
Sex	0.476	0.219-1.037	0.064	0.872	0.337-2.255	0.778	-0.644	-1.414-0.125	0.102	-0.105	-1.025-0.814	0.822
Lobes	0.960	0.733-1.256	0.764	0.922	0.684-1.241	0.591	-0.053	-0.321-0.215	0.698	-0.089	-0.379-0.201	0.547
Pathology	4.170	1.747-9.953	<0.001	7.467	2.333-23.901	0.001	1.308	0.441-2.175	0.017	1.766	0.661-2.871	0.002
T stage	1.040	0.780-1.386	0.791	1.601	1.099-2.333	0.014	0.060	-0.228-0.347	0.685	0.421	0.065-0.778	0.021
Calcification	0.432	0.186-1.002	0.043	0.392	0.159-0.966	0.042	-0.862	-1.701-0.023	0.037	-0.905	-17.840-0.026	0.044

OR, odds ratio; CI, confidence interval; Coef., coefficient.

CLNS were confirmed to have 5 solely metastasized NCLNS and 6 patients with CLNS were confirmed to have 15 simultaneously metastasized NCLNS. Among patients with NCLNS, 19 had 1 solely metastasized NCLNS and 6 patients had 2 simultaneously metastasized CLNS. In patients with CLNS, 8 patients had 1 solely metastasized CLNS and 6 patients had 2 simultaneously metastasized CLNS. Moreover, 5 patients had 1 solely metastasized NCLNS, and there 2 patients had 2, 1 patient had 3 and 2 patients had 4 simultaneously metastasized NCLNS. All patients were diagnosed as M0. The differences in clinicopathological characteristics, including age, sex, surgical lobes, pathology, tumor size, T and N, were not significant between patients with CLNS and NCLNS. No patient died intraoperatively or within 30 days after surgery.

Metastatic ratio of patients and LNS. The metastatic ratio of patients and LNS between the CLNS and non-CLNS groups is presented in Table II. On a per-patient basis, the differences in metastatic ratios were not significant between patients with CNLS and NCLNS, neither in the all-patient group (20.313 vs. 27.473%; $P=0.308$) nor in the patient group with solely CLNS or NCLNS metastasized (15.000 vs. 27.473%; $P=0.073$). However, on a per-nodal station basis, the metastatic ratios of patients with CLNS were all lower than those with NCLNS, not only in the all-LNS group (9.009 vs. 21.983%, $P=0.004$) but also in the LNS group which in patients with solely CLNS or NCLNS (9.009 vs. 21.678%; $P=0.009$) and in the patients with CLNS (9.009 vs. 22.472%; $P=0.010$).

Predictive factors of LNS metastasis. On a per-patient basis, pathology (odds ratio; OR=4.170; $P<0.001$) and calcification (OR=0.432; $P=0.043$) was identified as a predictive factor of metastasis by single-factor logistic analysis. Pathology (OR=7.467; $P=0.001$), T (OR=1.601; $P=0.014$) and calcification (OR=0.392; $P=0.042$) were identified as independent prognostic factors by multi-factor logistic analysis. On a per-station basis, pathology (Coefficient; Coef.=1.308; $P=0.017$) and calcification (Coef.=-0.862; $P=0.037$) remained a prognostic factor following single-factor ologit analysis. Pathology (Coef.=1.766; $P=0.002$), T (Coef.=-0.421; $P=0.021$) and calcification (Coef.=-0.905; $P=0.044$) were identified as independent prognostic factors by multi-factor ologit analysis (Table III). Fig. 2 demonstrates the ability of T, pathology and calcification to predict 1 (Fig. 2A) and 2 (Fig. 2B) LNS metastasis.

Impacts of CLNS on surgical outcomes. Although the number of LNs resected in the patients with CLNS was the same as that in the patients with NCLNS ($P=0.446$), a significantly higher number of patients with CLNS ($P=0.006$) than with NCLNS received the originally scheduled thoracotomy (51.56 vs. 37.6%) or conversion from VATS to thoracotomy (14.06 vs. 4.40%); these patients were also associated with a higher time cost (235.516±47.685 vs. 185.330±30.256 min; $P<0.001$) and blood loss (334.063±359.655 vs. 159.341±113.752 ml; $P<0.001$; Table IV).

Discussion

It is well known that systemic mediastinal nodal dissection is an integral part of radical surgery for lung cancer and is

Table IV. Differences in surgical outcomes between patients with CLNS and NCLNS.

Surgical outcomes	NCLNS	CLNS	P-value
Surgery, n (%)			0.006 ^a
VATS	53 (58.24)	22 (34.38)	
Conversion	4 (4.40)	9 (14.06)	
Thoracotomy	34 (37.36)	33 (51.56)	
Operating time, min (mean ± SD)	185.330±30.256	235.516±47.685	<0.001 ^b
Blood loss, ml (mean ± SD)	159.341±113.752	334.063±359.655	<0.001 ^b
Number of LN dissected, n (mean ± SD)	22.242±6.664	21.688±6.434	0.446 ^b

^aAnalyzed by multinomial logistic regression; ^bAnalyzed by two-sample Wilcoxon rank-sum (Mann-Whitney) test when the variances were not equal. CLNS, calcified lymph node station; LN, lymph node; NCLNS, non-calcified LN station; VATS, video-assisted thoracic surgery.

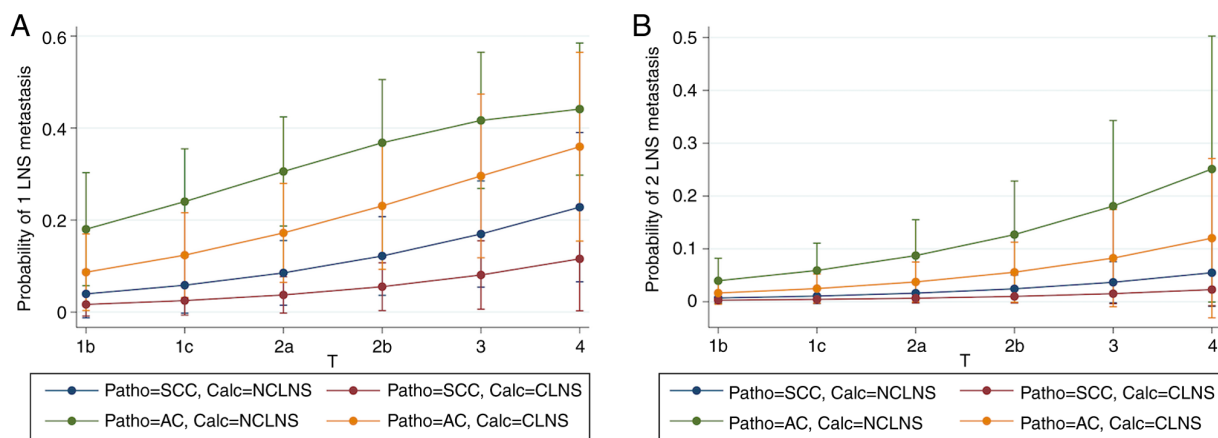


Figure 2. Predictive ability of T stage, pathology type and calcification status to predict (A) 1 or (B) 2 LNS metastasis. Vertical bar, 95% confidence intervals. AC, adenocarcinoma; Calc, calcification; CLNS, calcified lymph node station; LNS, lymph node stations; NCLNS, non-calcified lymph node stations; Patho, pathology; SCC, squamous cell carcinoma.

associated not only with pathological N staging and the selection of subsequent treatment strategies, but also with patient prognosis. In a previous study, mediastinal CLNs were commonly observed in the preoperative CT scans of patients with NSCLC, since they resided in an area with a high prevalence of tuberculosis (21). A total of 64 patients (41.29%) were found to have 111 CLNS. Although CLNs are generally thought to be benign (8,9), a number of case reports (10,11) have confirmed that primary lung cancer could metastasize to CLNS. In a small sample size study, Nakanishi *et al* (13) evaluated 72 consecutive patients with CLNS detected on preoperative CT who underwent pulmonary resection for primary lung cancer. A total of 354 LNs, including 101 CLNs, were evaluated. The frequency of metastasis to CLNS was 19.4% (14/72 patients) on a per-patient basis and 18.8% (19/101 CLNS) on a per-nodal station basis. In the present study, the metastatic ratio of CLNS was 15.000% (9/60 patients) on a per-patient basis and 9.009% (10/111 CLNS) on a per-nodal station basis, suggesting that metastasis to CLNS was not rare in patients with NSCLC. To the best of our knowledge, the mechanisms of metastasis to CLNS remain unclear. Nakanishi *et al* (13) hypothesized that cancer secreting calcium metastasized to previously existing CLNS and NCLNS (11). From the pathological findings of previous studies (3-5), it can

be concluded that cancer metastasizes to tissues surrounding the CLN but not to the calcified body itself, since the reported metastatic LNs were all psammomatous (10,11), and no metastases occurred in single and large CLNS which was single and with major size (26/101) (13). However, the precise mechanisms of metastasis to CLNS should be investigated by future studies.

Although, on a per-station basis, the metastatic ratios of patients with CLNS were lower than those of patients with NCLNS [not only in the all-LNS group (9.009 vs. 21.983%; $P=0.004$) but also in the LNS groups which in patients with solely CLNS or NCLNS (9.009 vs. 21.678%; $P=0.009$) and in the patients with CLNS (9.009 vs. 22.472%; $P=0.010$)] and CLNS was an independent risk reduction factor on both a per-patient (OR=0.392; $P=0.0402$) and a per-nodal station basis (Coef.=−0.905; $P=0.044$), the metastatic ratios were comparable on a per-patient basis [both in the all-patient group (20.313 vs. 27.473%; $P=0.308$) and in the patient group with solely CLNS or NCLNS (15.000 vs. 27.473%; $P=0.073$)]. These results suggested that CLNS should be dissected in addition to NCLNS to achieve radical dissection, although the results of the present and a previous study (13) found that CLNS is less likely to metastasize than NCLNS. Furthermore, as stated in a previous study (22), it was also confirmed that

T stage and adenocarcinoma were independent risk factors for LNS metastasis.

Previous studies have confirmed that dissecting CLNS is challenging and time-consuming (14,15). However, utmost efforts were made for their thorough removal. Thus, the number of LNs resected was not significantly different between patients with NCLNS and those with CLNS (22.242 ± 6.664 vs. 21.688 ± 6.434 ; $P=0.446$). However, more time was spent (235.516 ± 47.685 vs. 185.330 ± 30.256 min; $P<0.001$) and more blood was lost (334.063 ± 359.655 vs. 159.341 ± 113.752 ml; $P<0.001$) during the surgery of patients with CLNS. Furthermore, since several studies had demonstrated that CLNS could predict intraoperative conversion from VATS to thoracotomy during lobectomy due to adhesion between CLNS and hilar structures (14,15,17,23), it was found that a significantly higher number of patients with CLNS than with NCLNS received the originally scheduled thoracotomy (51.56 vs. 37.36%) or underwent conversion from VATS to thoracotomy (14.06 vs. 4.405%). These results were consistent with those of the study by Byun *et al* (17), in which 69/276 patients (25.00%) received conversion from VATS to thoracotomy, of whom 40.58% (28/69) had CLNS. CLNS was also confirmed in that study to be an independent risk factor for conversion (OR=2.67; $P=0.020$).

The present study was not without its limitations. It failed to further explore the associations between the characteristics of CLNS and metastasis, such as calcification type (focal or diffuse calcification) and LN size, which were not classified due to the small sample size. Further investigation in a study with a larger sample size is encouraged to clarify these associations.

In conclusion, although CLNS are a risk reduction factor for metastasis and their dissection is time- and blood-consuming in patients with NSCLC, their thorough removal is advised, since metastases were identified in ~15% patients and 9% CLNS.

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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

LL, XW, MZ, SY, YW, HX and XD analyzed and interpreted the data. LL, XW, MZ and HX were major contributors in writing the manuscript. LL, SY, YW and XD confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by our hospital's review board (approval no. 2020-244, the Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou, China). Written informed consent was obtained from all individual participants included in the study.

Patient consent for publication

Patients signed the informed consent form regarding the publication of their data and images.

Competing interests

The authors declare that they have no competing interests.

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