

Study on the difference and regularity of tongue images in 309 patients with different pathological stages of non-small cell lung cancer

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Abstract.

BACKGROUND: Tongue diagnosis is a crucial traditional Chinese medicine (TCM) inspection method for TCM syndrome differentiation and treatment.

OBJECTIVE: The primary research focus was on tongue image characteristic parameters of patients with non-small cell lung cancer (NSCLC). Analysis of the tongue image parameters of various pathological stages of NSCLC provides technical support for establishing an integrated Chinese and Western auxiliary diagnosis and efficacy evaluation medicine system for lung cancer that integrates tongue image features.

METHODS: Tongue image characteristics of 309 patients with NSCLC and 206 controls were collected and analyzed clinically. The *T*-test or rank sum test and logistic regression analysis were applied to analyze the characteristics of tongue image indicators of different pathological stages of NSCLC.

RESULTS: There were differences in tongue image characteristics in the NSCLC group compared to the control group. The tongue quality and brightness of the tongue coating in the NSCLC group increased, the red component was reduced, the tongue coating thickened, and the yellow component increased compared to the healthy control group. A comparison of tongue image indexes of NSCLC in different pathological stages showed that stage IV had lower TB-b and higher TB-a than stage I. In addition, stage IV had lower TB-b than stage II + III, showing an increase in the blue and red components of the tongue in stage IV and the appearance of cyanotic tongue features.

CONCLUSION: The tongue image characteristics of NSCLC patients differed from those of the control group. Tongue imaging indicators can reflect the characteristics of tongue images of patients with NSCLC. The tongue image characteristics of patients with stage IV lung cancer are bluish and purple compared with those with stage I, II, and III. It is suggested that the tongue's image characteristics can be used as a reference for the pathological classification of NSCLC and judgment of the disease process.

Keywords: Non-small cell lung cancer, tongue image, image features, pathological staging, traditional Chinese medicine

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1. Introduction

Malignant tumors are significant diseases that seriously threaten human life and health. The latest statistics show that China ranks first in the world in terms of new cancer incidence and mortality, with 4.57 million new cancer cases in China, accounting for 23.7% of new cases worldwide (19.29 million new patients worldwide), and 3 million cancer deaths, accounting for 30% of total cancer deaths (9.96 million cancer deaths worldwide). Among these, lung cancer is China's most common malignant tumor, with 820,000 new cases and 710,000 deaths. According to pathology, lung cancer can be classified into two categories: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), of which NSCLC is the most common [1,2,3]. There are an increasing numbers of studies on lung cancer prevention, diagnosis, and treatment, especially NSCLC. Tongue diagnosis is a crucial traditional Chinese medicine (TCM) inspection method for TCM syndrome differentiation and treatment. Tongue diagnosis identifies the location and nature of the disease, speculates on the cause and mechanism of the disease, and suggests the progression and prognosis of the disease [4]. In the past 30 years, many researchers have observed the tumor of the tongue characteristics. In 1987, the research results of the Cooperative Group of Traditional Chinese Medicine and Western Medicine Cancer Professional Committee recommended specific rules for the changes in tongue pictures of patients with tumors [5]. However, the clinical application of tongue diagnosis is affected by the external environment and doctors' experience. Therefore, the theory and clinical experience of tongue diagnosis have been systematically summarized. The use of modern science and technology to establish an objective standard for tongue diagnosis is a significant challenge in expanding its application scope of tongue diagnosis. Since the 1990s, with the development of computer digital image processing technology and the progress of objectification of tongue diagnosis, many achievements have been made in the standardization of tongue image acquisition in Traditional Chinese Medicine Quantification [6,7,8,9,10,11,12,13,14,15]. Researchers have increasingly applied objective tongue diagnosis to diagnose and treat clinical diseases and evaluate the curative effect based on research on classification and recognition.

This study describes the tongue image characteristics of non-small cell lung cancer with datable tongue image indices. Further, it analyzes the tongue image characteristics of NSCLC patients with different tumor node metastasis (TNM) stages. We introduced image indices that objectively reflect the diagnostic information of tongue images based on clinical observations. We provided technical support for establishing a combined Chinese and Western medicine lung cancer diagnosis and treatment evaluation system incorporating data-based information on tongue diagnosis.

2. Materials and methods

2.1. Clinical information

2.1.1. Study design and participants

The NSCLC group included 316 patients hospitalized in the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine oncology ward between October 2016 and November 2018. Additionally, a total of 553 people were screened from September to December 2017 at the health check-up center of Shuguang Hospital as a control group. Tongue images of the patients were collected using a uniform tongue diagnostic device. A flowchart of the process is shown in Fig. 1.

2.1.2. Diagnostic criteria

(1) Diagnostic criteria for non-small cell lung cancer

The National Comprehensive cancer network (NCCN) published guidelines for non-small cell lung

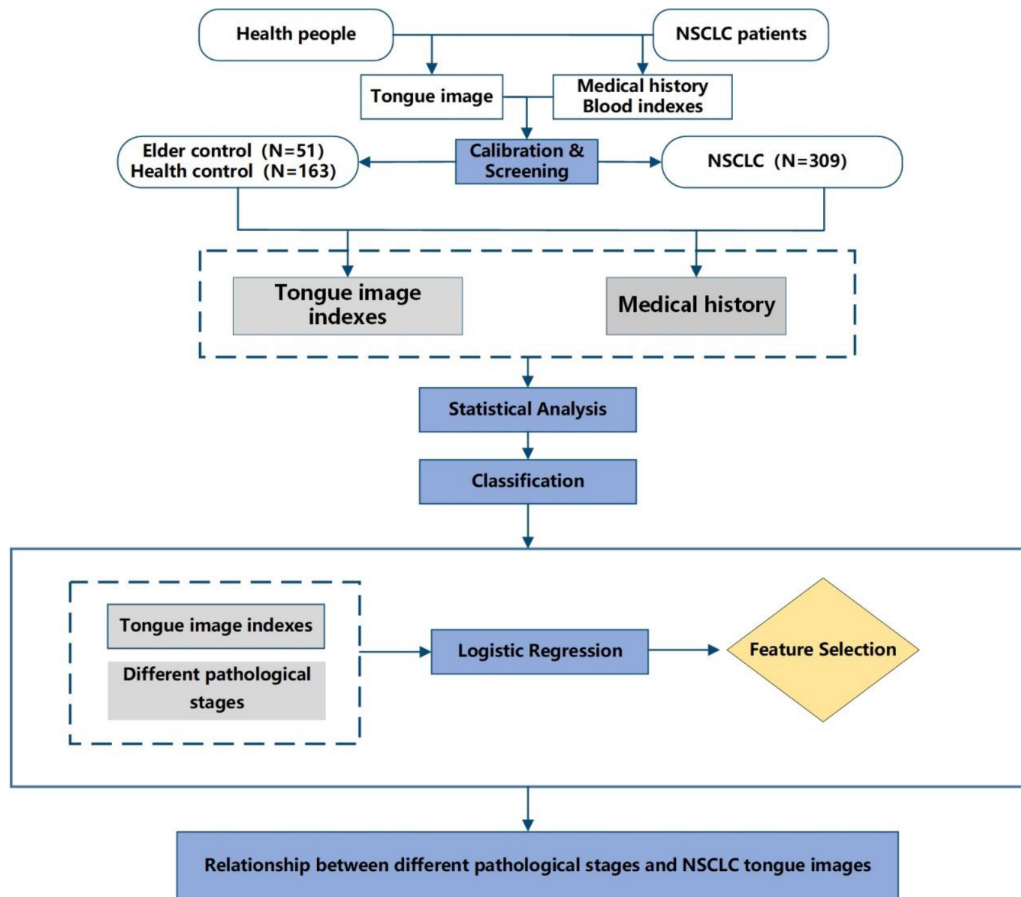


Fig. 1. Flowchart.

cancer in 2017 and the principles of diagnosis and evaluation of clinical guidelines for diagnosis and treatment (2011 edition) [16,17].

(2) Diagnostic criteria for the TNM staging of non-small cell lung cancer

In this study, according to the TNM staging standard (8th edition), the Union for International Cancer Control (UICC) issued in 2018 [18], only patients with NSCLC were observed, and no clinical intervention was carried out [16]. The American Joint Committee on Cancer (AJCC) cancer staging manual [19]. Patients with non-small cell tumors were classified into I, II, III, and IV stages without further detailed division.

2.1.3. Inclusion criteria and exclusion criteria

Inclusion and exclusion criteria in the control group

(1) Inclusion criteria for the control group:

- a. There was no history of cancer diagnosis, no acute disease diagnosis within three months, and no treatment according to the clinical diagnostic criteria of the disease.
- b. Age between 25–85 years old;
- c. Unlimited gender.

(2) Exclusion criteria for the control group:

- a. Those who did not meet the inclusion criteria of the control group;
- b. Pregnant or lactating women;
- c. Unable to cooperate with researchers because of subjective and objective reasons.

Inclusion and exclusion criteria in the NSCLC group

(1) Inclusion criteria for patients with non-small cell lung cancer:

- a. The diagnosis is precise;
- b. The age is between 25–85;
- c. There is no restriction on gender.

(2) Exclusion criteria for patients with non-small cell lung cancer:

- a. Those who did not meet the inclusion criteria for NSCLC;
- b. Lung cancer is complicated with other significant diseases;
- c. Pregnant or lactating women;
- d. Unable to cooperate with researchers because of subjective and objective reasons.

2.2. Experimental instruments and methods

2.2.1. Experimental apparatus

The TDA-1 digital tongue diagnosis instrument was used as the tongue image acquisition equipment (developed by the Laboratory of Intelligent Processing of TCM Diagnostic Information, Shanghai University of Traditional Chinese Medicine, patent number: CN201814562U) [20]. The tongue image diagnosis analysis system (TDAS v2.0) developed by the TCM Diagnostic Information Intelligent Processing Laboratory, Shanghai University of Traditional Chinese Medicine (Software Copyright:2018SR033451) was used to obtain relevant data. All tongue image collection and inquiry studies were completed by professional TCM or integrated TCM and Western medicine personnel who had received standardized training to ensure the consistency and authenticity of data collection and interpretation, and to minimize deviation. The TDA-1 digital tongue diagnosis instrument is shown in Fig. 2, and the corresponding tongue image analysis system TDAS v2.0 is shown in Fig. 3.

2.2.2. Experimental methods

Tongue image acquisition

- (1) The tongue images were collected before breakfast from 6:15 to 7:15 in the morning.
- (2) The process of tongue image acquisition was based on the standard procedure of tongue image acquisition developed by the Laboratory of Intelligent Diagnosis Technology, Shanghai University of Traditional Chinese Medicine.

Feature extraction of tongue image

The special tongue analysis software TDAS v2.0 extracts all tongue indices. The tongue image color index is derived from the International Commission on Illumination Lab color space (CIELab). The pixel's brightness is represented with "L," and its value range is [0–100], representing pure black to pure white. The range from red to green is indicated with "a," and its value range is [127–128]. "b" denotes the range from yellow to blue, the value range is [127–128]; the diagrams of Lab color space are shown in Fig. 4. Lab color space is a type of uniform color space that is a color space independent of equipment. It is a color system based on physiological characteristics. In other words, Lab color space uses a digital

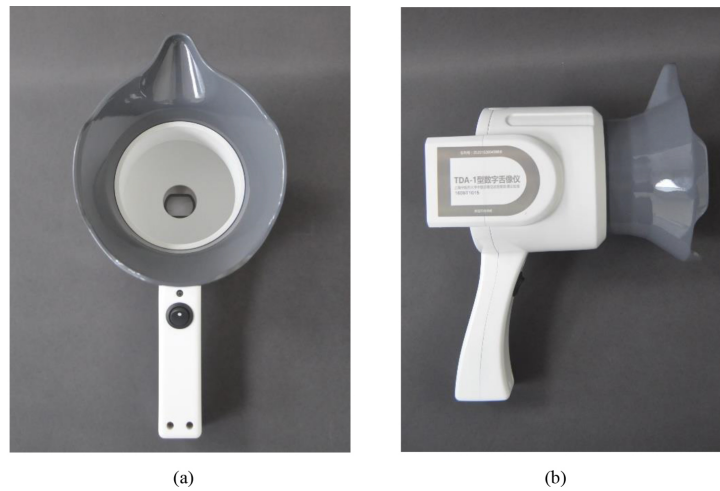


Fig. 2. TDA-1 digital tongue diagnosis instrument: (a) front view; (b) profile view.

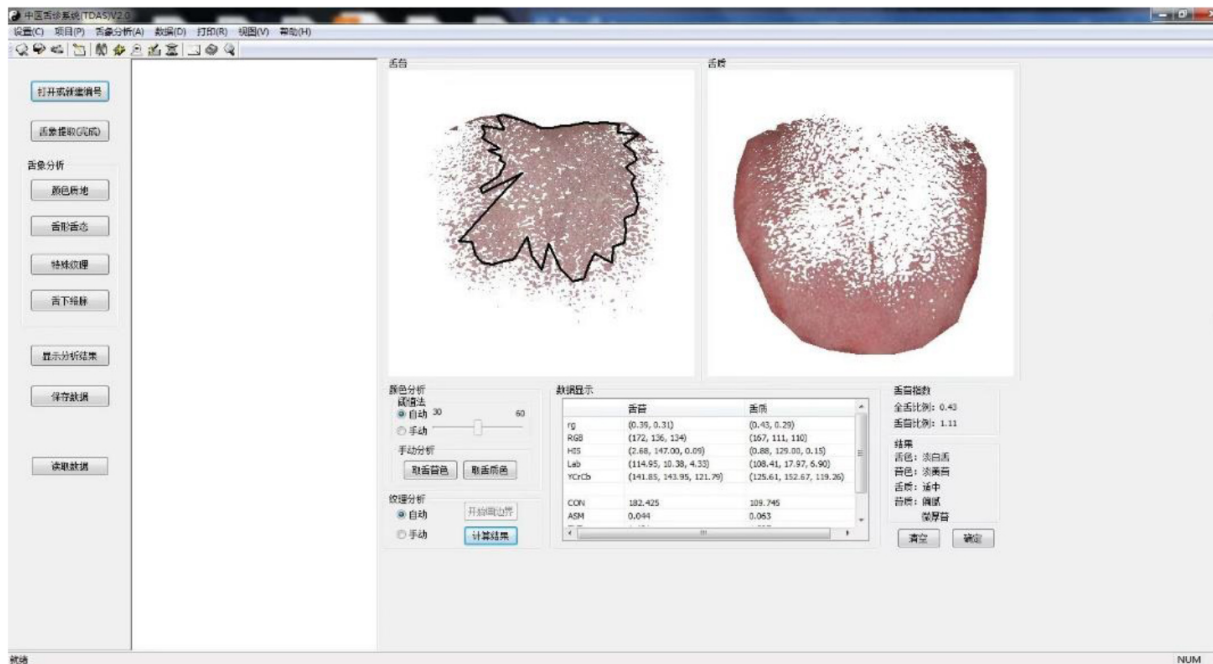


Fig. 3. Tongue image diagnosis analysis system (TDAS v2.0) of TDA-1 digital tongue diagnosis instrument.

method to describe human visual perception. It is a color space suitable for the clinical description of tongue features [21]. It has been used in tongue diagnosis by several researchers [22,23]. Previous studies have shown that the Lab color space best describes and distinguishes the tongue color of Traditional Chinese Medicine. Previous studies have shown that the lab color space best describes and differentiates tongue colors in TCM. The four tongue colors (pale red, pale white, red-red, and blue-violet) can be distinguished by the a-value and b-value. It is recommended that the L^*a^*b color space is most suitable for TCM's description and differentiation of tongue colors [24]. In this study, we used the Lab color

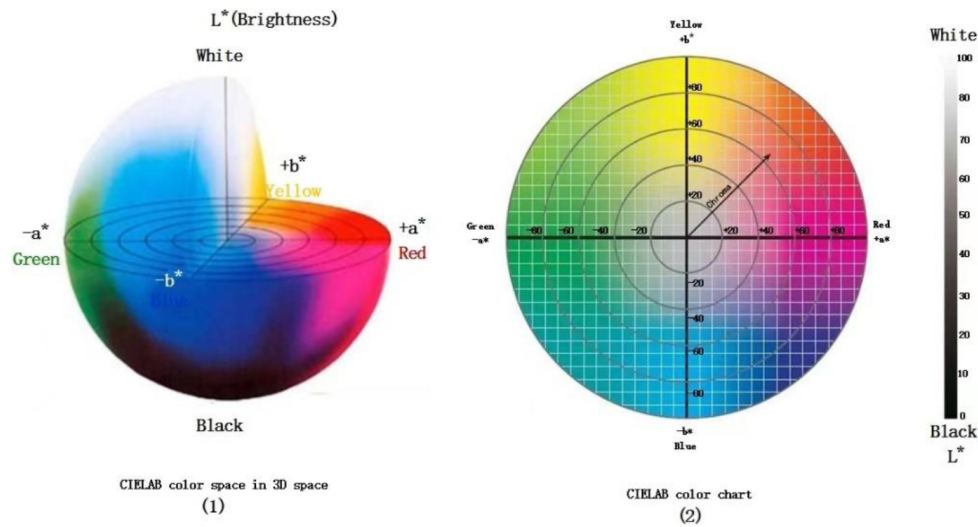


Fig. 4. Lab space color.

space index as the primary reference index to describe tongue color, in which L (lightness), a (red-green axis), b (yellow-blue axis), tongue coating index: perAll (perAll = the ratio of coated tongue area to total tongue area), and perPart (the ratio of effective pixels of tongue body to the effective pixel of tongue coating). Texture indices include CON (Contrast), ASM (Angular Second Moment), ENT (Entropy), and MEAN. The image index of the tongue body (TB) includes the color index (TB-L, TB-a, and TB-b) and texture index (TB-CON, TB-ENT, TB-ASM, and TB-MEAN). The image indexes of tongue coating (TC) included the color index (TC-L, TC-a, TC-b), texture index (TC-CON, TC-ENT, TC-ASM, TC-MEAN), and tongue coating index (perAll, perPart).

2.2.3. Statistical methods

Data conforming to a normal distribution were expressed as mean (standard deviation) and Mean (SD). Data not conforming to a normal distribution were expressed as median (25th percentile, 75th percentile) and Median (IQR). Measures were compared between three or two groups for normally distributed data using analysis of variance (ANOVA), multiple comparison tests, or *t*-tests. Kruskal-Wallis analysis of variance (ANOVA) or Mann-Whitney U-test was used for non-normally distributed data. Count data were expressed as percentages (%) and compared using Pearson's χ^2 test or Fisher's exact test. One-way conditional logistic regression analysis was performed on statistically different factors by the *t*-test and χ^2 test. A factor was considered a protective factor when the dominance ratio (odds ratio, OR) was less than one and a risk factor when the OR value was > 1 . Factors that were statistically different by the *t*-test and χ^2 test were subjected to one-way conditional logistic regression analysis. Excel and python 3.0 were used for data matching, merging, and sorting; SPSS version 26.0 (IBM Corp., Armonk, NY, USA) statistical software was used for processing. All test results were two-tailed ($P < 0.05$). GraphPad Prism 8 software was used to draw violin plots of the tongue data.

3. Experimental results

3.1. General information

Age is an essential factor affecting lung cancer incidence [19]. Therefore, according to the inclusion

Table 1
Comparison of essential information between NSCLC and control group [*n* (%), median (IQR)]

Project	Healthy control group <i>n</i> = 163	Elderly control group <i>n</i> = 51	NSCLC group <i>n</i> = 309	Total
Gender <i>n</i> %				
Female	84 (51.5)	23 (45.1)	169 (54.7)	192 (53.3)
Male	79 (48.5)	28 (54.9)	140 (45.3)	168 (46.7)
Age median (IQR)	32 (28–40)	61 (58–65)	64 (57.50–70.00)*	

*Statistically significant difference ($P < 0.05$). Pearson χ^2 test was used for categorical data, and the Mann-Whitney U test was used for measurement data.

Table 2
History of NSCLC patients

Project	Number
Total (<i>n</i>)	309
Age, median (IQR)	64 (57.50–70.00)
The course of lung cancer, median (IQR)	14.317 (5.233–24.567)
Gender, <i>n</i> %	
Female	169 (54.7)
Male	140 (45.3)
Pathological type, <i>n</i> %	
Adenocarcinoma	264 (85.4)
Squamous cell carcinoma	45 (14.6)
Pathological stage, <i>n</i> %	
I	137 (44.3)
II	20 (6.5)
III	35 (11.3)
IV	117 (37.9)
At the same time, <i>n</i>	58 (18.77)
EGFR (+), <i>n</i> %	62 (20.06)
Smoking history, <i>n</i> %	
No	235 (79.9)
Yes	59 (20.1)
Family history, <i>n</i> %	
Nothing	272 (92.5)
Yes	22 (7.5)
Hypertension, <i>n</i> %	
No	223 (72.9)
Yes	83 (27.1)
Diabetes, <i>n</i> %	
No	275 (90.2)
Yes	30 (9.8)
Hyperlipidemia, <i>n</i> %	
No	297 (97.1)
Yes	9 (2.9)
Operation condition, <i>n</i> %	
No operation	81 (26.2)
Operation	228 (73.8)
Chemotherapy, <i>n</i> %	
Not used	151 (48.9)
Used	158 (51.1)
Used in a month	21 (6.9)
Targeted therapy, <i>n</i> %	
No	256 (82.8)
Yes	53 (17.2)

Note: Owing to the lack of clinical data, the number of people in some items is not equal to the total number.

criteria and physical examination results of the control group, 51 cases of the elderly control group older than 55 years were selected, and each was sampled once. At the same time, a total of 316 NSCLC patients were sampled, a total of 1257 images of NSCLC patients, excluding 6 cases of unclear stage classification, two times of surgery, finally including 309 people, for a total of 1235 tongue image data. The three groups' basic information is shown in Tables 1 and 2.

Table 1 shows that the gender and age distribution of the NSCLC group was not statistically different ($P > 0.05$) compared with the elderly control group. However, compared with the healthy control group, the age of the NSCLC group was different ($P < 0.05$), and the gender distribution was not different ($P > 0.05$).

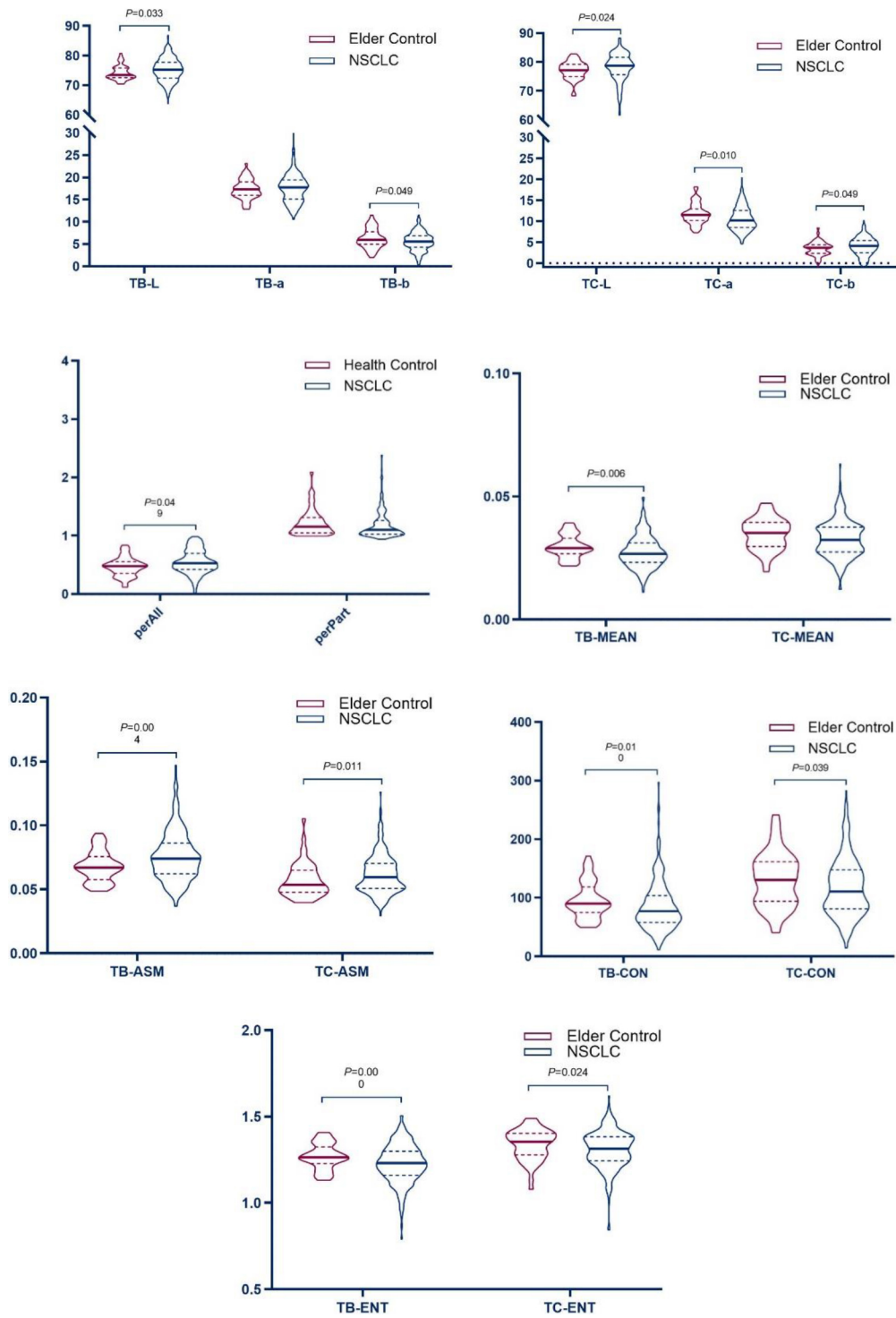


Fig. 5. Violin plot of tongue data between the Elder Control and NSCLC.

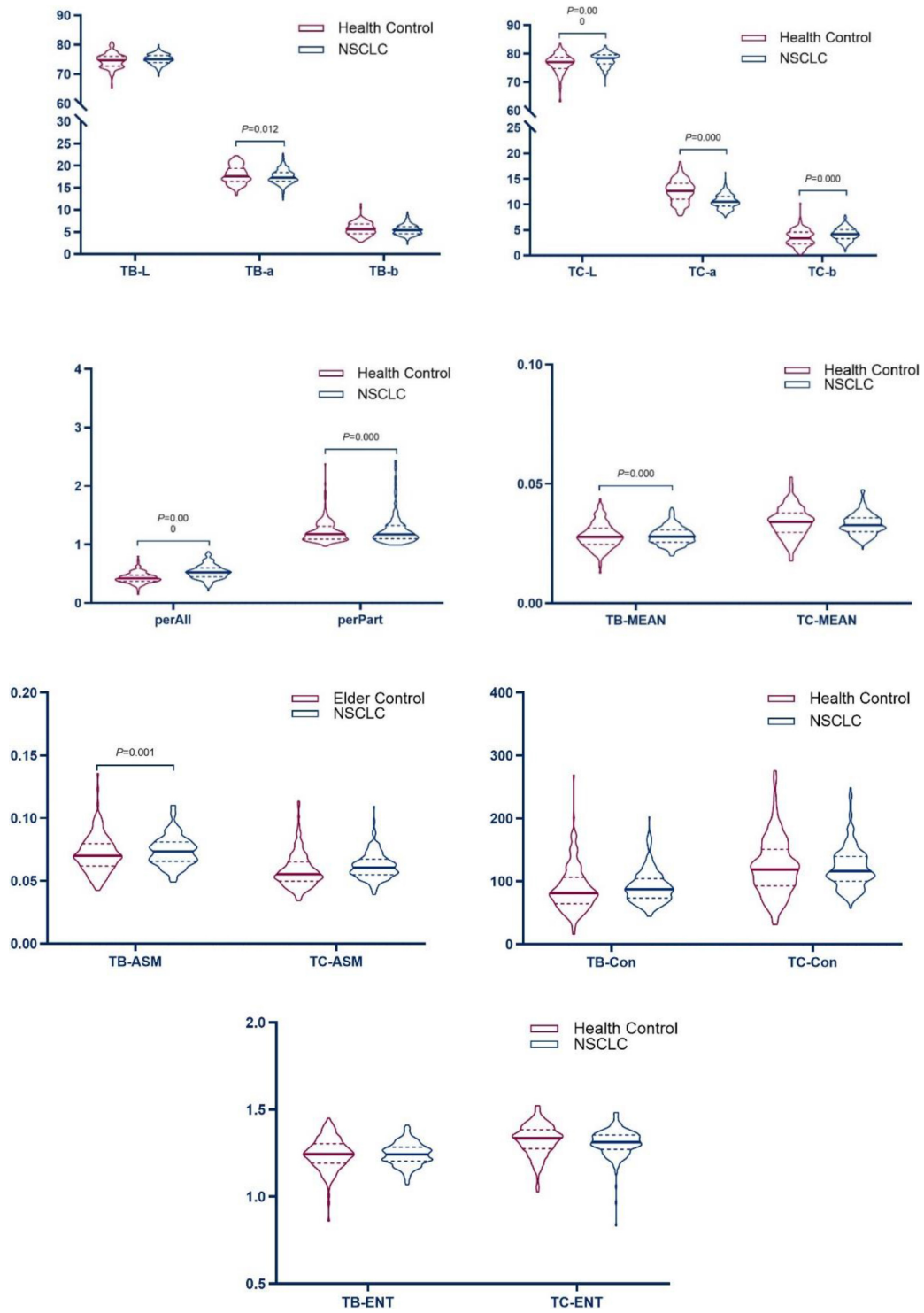


Fig. 6. Violin plot of tongue data among the Health Control and NSCLC.

Table 3

Comparison of tongue image indexes between the NSCLC group and elderly control group [mean (SD), median (IQR)]

Tongue index			Elderly control group N = 51	NSCLC group N = 309	t/Z	P
TB	L*a*b	L	73.47 (72.62–75.87)	75.14 (72.48–77.62)	–2.136	0.033
		a	17.34 (2.24)	17.63 (3.16)	0.790	0.430
		b	6.25 (2.2)	5.61 (2.11)	–1.980	0.049
	Texture index	CON	90.12 (74.96–118.64)	77.29 (57.57–104.8)	–2.582	0.010
		ENT	1.27 (0.07)	1.23 (0.11)	–3.440	0.000
		ASM	0.07 (0.06–0.08)	0.07 (0.06–0.09)	–2.898	0.004
	MEAN	0.03 (0.03–0.03)	0.03 (0.02–0.03)	–2.743	0.006	
TC	L*a*b	L	77.22 (74.99–79.25)	78.72 (75.41–81.42)	–2.255	0.024
		a	11.51 (10.2–12.92)	10.28 (8.5–12.62)	–2.592	0.010
		b	3.68 (2.33–4.36)	4.03 (2.56–5.41)	–1.972	0.049
	Tongue coating index	perAll	0.48 (0.35–0.56)	0.52 (0.42–0.68)	–2.795	0.049
		perPart	1.16 (1.06–1.32)	1.11 (1.04–1.3)	–1.455	0.146
	Texture index	CON	130.49 (94.05–161.4)	109.67 (81.23–147.33)	–2.067	0.039
		ENT	1.35 (1.28–1.4)	1.31 (1.24–1.38)	–2.256	0.024
		ASM	0.05 (0.05–0.07)	0.06 (0.05–0.07)	–2.557	0.011
		MEAN	0.03 (0.01)	0.03 (0.01)	–2.000	0.050

Note: The *t*-test or Mann-Whitney U test was used. $P < 0.05$, the difference was statistically significant.

Table 4

Comparison of tongue image indexes between the NSCLC group and healthy control group [mean (SD), median (IQR)]

Domain	Color space	Index	Healthy control group N = 163	NSCLC group N = 1235	t/Z	P
Tongue	L*a*b	TB-L	74.08 (6.35)	75.08 (3.79)	–1.966	0.051
		TB-a	17.96 (2.02)	17.49 (3.46)	2.522	0.012
		TB-b	5.7 (1.46)	5.48 (2.40)	1.656	0.099
	Texture index	TB-CON	81.55 (64.38–106.37)	85.39 (62.17–112.87)	–0.603	0.546
		TB-ENT	1.24 (1.19–1.3)	1.25 (1.18–1.32)	–0.342	0.732
		TB-ASM	6.45 (5.05–7.58)	6.92 (5.97–7.83)	–3.415	0.001
	TB-MEAN	2.82 (2.45–3.2)	2.61 (1.65–3.17)	–3.832	0.000	
Tongue coating	L*a*b	TC-L	76.64 (3.32)	77.94 (4.89)	–4.428	0.000
		TC-a	12.61 (2.22)	10.61 (2.88)	10.433	0.000
		TC-b	3.41 (2.4–4.61)	4.23 (2.55–5.74)	–4.217	0.000
	Tongue coating index	perAll	0.42 (0.37–0.48)	0.51 (0.42–0.65)	–7.996	0.000
		perPart	1.18 (1.09–1.31)	1.12 (1.04–1.28)	–4.176	0.000
	Texture index	TC-Con	118.9 (92.99–151)	114.52 (85.15–150.91)	–0.667	0.505
		TC-ENT	1.34 (1.28–1.38)	1.32 (1.26–1.39)	–1.084	0.279
		TC-ASM	5.55 (4.85–6.46)	5.51 (4.53–6.64)	–0.807	0.420
		TC-MEAN	0.03 (0.03–0.04)	0.03 (0.03–0.04)	–0.395	0.693

Note: The *t*-test or Mann-Whitney U test was used. $P < 0.05$, the difference was statistically significant.

3.2. Comparison of tongue features between NSCLC patients and non-tumor patients

Tongue images of 309 NSCLC cases were compared with those of 51 elderly controls to investigate the differences in tongue image characteristics between patients with and non-tumor patients. A light red tongue characterizes a healthy tongue with a thin white coating. Therefore, the differences between 1235 tongue images of NSCLC patients were compared with 163 tongue images of healthy controls with “light red tongue and thin white coating” to compare the tongue images of NSCLC patients and healthy tongue images. The results are shown in Tables 3–6.

Table 3’s results showed that the tongue image indexes TB-L, TB-ASM, TC-L, TC-b, TC-ASM, and

Table 5
Logistic analysis of tongue image index between the NSCLC and healthy control

Index	B	OR	95% CI.		P
			Lower limit	Upper limit	
Gender	-0.520	0.594	0.250	1.411	0.238
Age	0.242	1.274	1.212	1.340	0.000
perAll	5.982	396.041	16.060	9766.617	0.000
TC-L	-0.161	0.851	0.731	0.991	0.038
TC-a	-0.389	0.678	0.539	0.852	0.001

Note: The dependent variables were the NSCLC group and healthy control group (0 = healthy control group, 1 = NSCLC group), the control variables included gender (1 = female, 2 = male) and age, and the independent variables included TB-L, TB-a, TB-b, TCL, TC-a, TC-b, TBASM, TCASM, and perAll. None of the variables had collinearity problems ($VIF < 10$). Only tongue image indices that could enter the regression equation were included in the table ($P < 0.05$). Forward: The LR method was used.

perAll in the NSCLC group were higher than those in the elderly control group ($P < 0.05$). However, TB-b, TB-CON, TB-ENT, TB-MEAN, TC-a, TC-CON, and TC-ENT were lower in the NSCLC group than in the elderly control group ($P < 0.05$).

The results showed that the tongue image indices TC-L, TC-b, perAll, and TB-ASM in the NSCLC tongue group were higher than those in the healthy control group ($P < 0.05$). Conversely, TB-a, TC-a, TB-MEAN, and perPart were lower than those in the healthy control group, with statistical significance ($P < 0.05$).

The results showed that, compared with the control group, the brightness of the tongue body and tongue coating in the NSCLC group increased, the red component decreased, the thickness and the yellow component of the tongue coating increased, and the tongue coating was more greasy.

3.3. Analysis of tongue image characteristics between the NSCLC group and the healthy control group

The presence of characteristic differences in tongue image indexes between the NSCLC group (309 people) and the healthy control group (163 persons) was analyzed to control the influence of baseline factors on tongue image because of the difference in age distribution between the NSCLC group and the healthy control group. The differences in tongue image characteristics between the NSCLC and healthy control groups were analyzed using binary logistic regression. The results are shown in Tables 5 and 7, respectively.

The results in Table 5 show that after controlling for the influence of sex and age, the tongue image indicators perAll, TC-L, and TC-a in the NSCLC and healthy control groups were specific between the two groups ($P < 0.05$). Compared to the healthy control group, perAll was a risk factor for the NSCLC group ($OR > 1$), and TC-L and TC-a were protective factors ($OR < 1$). The ranking of the influence of the three tongue image indices on the classification of NSCLC and healthy control group was $perAll > TC-L > TC-a$ by calculating the OR value, indicating that perAll is the most specific index for classifying NSCLC patients' tongue images and healthy tongue images.

The results showed that the tongue coating index was the main difference in tongue image features between the NSCLC and healthy control groups. The tongue coating in the NSCLC group was thicker, the red component of the tongue coating was reduced, and the brightness was lower compared with the healthy control group. The above results showed that the tongue image index could reflect the difference

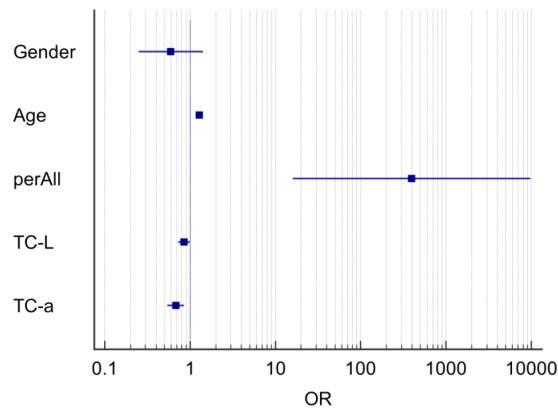


Fig. 7. Forrest plot of the NSCLC and healthy control.

between the tongue image of patients with NSCLC and normal tongue image data; therefore, it could be used to represent the change in tongue image characteristics of NSCLC patients.

3.4. Tongue image characteristics of different pathological stages of non-small cell lung cancer

Pathological staging plays an important role in the treatment and prognosis of NSCLC patients. Pathological staging is determined according to clinical and pathological factors, which play a key role in selecting treatment and prognosis. Therefore, this study analyzed the characteristics of tongue images of patients with NSCLC with different TNM stages.

Basic information on NSCLC patients with different pathological stages

The number of cases in stages II and III is small in clinical sampling, and both are in the middle stage of disease development. Nevertheless, the two are similar in terms of pathological and tongue manifestations. Therefore, the data of stage II and phase III patients were combined and analyzed and classified into three groups according to stages I, II + III, and IV. The basic information on the three groups is presented in Table 6.

3.5. Comparison of tongue image characteristics of patients with different pathological stages

(1) Three hundred and nine samples were classified into three groups according to different stages to study whether different pathological stages impact tongue images. The results are presented in Table 7.

The results in Table 7 show that the TB-a and TB-b in the stage IV group were significantly different from those in the stage I group and the II + III group ($P < 0.05$). Compared with the stage I group, TB-a increased, and TB-b decreased in the stage IV group; compared with the stage II + III group, TB-a increased in the stage IV group.

(2) Sex, age, smoking history, pathological classification, surgery, and course of the disease are different in different stages of patients, and they are the factors affecting the clinical staging and tongue manifestation. Therefore, we further analyzed the image indicators of tongue images in the three groups to study whether different pathological stages can independently affect the image characteristics of tongue images. Binary logistic regression analysis was used; Stage I and Stage II + III were used as the reference categories.

Table 6
Basic information on NSCLC patients with different pathological stages [*n* (%), median (IQR)]

Project		Stage I <i>N</i> = 137	Stage II + III <i>N</i> = 55	Stage IV <i>N</i> = 117	Total
The course of the disease: median (IQR)		8.067 (2.1–22.883)	12.05 (3.783–21.583)*	19.333 (11.35–39.492)*#	
Age median (IQR)		62 (56–69)	66 (62–71)*	64 (58–70)	
Gender, <i>n</i> %	Female	93 (67.9)	19 (34.5)*	57 (169)*	169 (54.7)
	Male	44 (32.1)	36 (65.5)*	60 (51.3)*	140 (45.3)
Smoking history, <i>n</i> %	No	114 (86.4)	36 (65.5)*	85 (79.4)*#	235 (79.9)
	Yes	18 (13.6)	19 (34.5)*	22 (20.6)*#	59 (20.1)
Family history, <i>n</i> % [▲]	Nothing	125 (97.7)	52 (94.5)	95 (88.8)	272 (92.5)
	Yes	7 (5.3)	3 (5.5)	12 (11.2)	22 (7.5)
Hypertension, <i>n</i> %	No	101 (33.0)	35 (11.4)	87 (28.4)	223 (72.9)
	Yes	34 (25.2)	20 (36.4)	29 (25.0)	83 (27.1)
Diabetes, <i>n</i> %	No	121 (39.7)	49 (89.1)	105 (91.3)	275 (90.2)
	Yes	14 (10.4)	6 (10.9)	10 (8.7)	30 (9.8)
Hyperlipidemia, <i>n</i> % [▲]	No	131 (96.3)	53 (96.4)	113 (98.3)	297 (97.1)
	Yes	5 (3.7)	2 (3.6)	2 (2.9)	9 (2.9)
Pathological classification	Adenocarcinoma	129 (94.2)	38 (69.1)*	97 (82.9)*	264 (85.4)
	Squamous cell carcinoma	8 (5.8)	17 (30.9)*	20 (17.1)*	45 (14.6)
Operation	No operation	9 (6.6)	18 (32.7)*	54 (46.2)*	81 (26.2)
	Operation	128 (93.4)	37 (67.3)*	63 (53.8)*	228 (73.8)
Chemotherapy	Not used	98 (71.5)	12 (21.8)*	41 (35.0)*	151 (48.9)
	Used	39 (28.5)	43 (78.2)*	76 (65.0)*	158 (51.1)
	Used within one month	3 (2.2)	5 (9.1)*	13 (11.1)*#	21 (6.8)

Note: * significantly different from stage I; # significantly different from stage II + III; ▲ the minimum expected cell count was less than 5, and Fisher's exact test was used. Pearson's χ^2 test was used for classified data, and the Mann-Whitney U test was used for measurement data. The difference was statistically significant ($P < 0.05$).

Table 7
Comparison of tongue image indexes in different pathological stages [mean (SD), median (IQR)]

Domain	Color space	Index	Phase I <i>N</i> = 137	Stage II + III <i>N</i> = 55	Stage IV <i>N</i> = 117
Tongue body	L*a*b	TB-L	75.48 (3.95)	75.29 (3.1)	74.74 (3.86)
		TB-a	17.21 (3.04)	16.95 (2.75)	18.45 (3.34)*#
		TB-b	5.88 (2)	6.17 (2.17)	5.03 (2.08)*
	Texture index	TB-CON	81.53 (58.65–108.53)	80.84 (58–105.66)	72.61 (57.06–100.71)
		TB-ENT	1.24 (0.11)	1.23 (0.11)	1.22 (0.11)
		TB-ASM	0.07 (0.06–0.09)	0.07 (0.06–0.09)	0.08 (0.06–0.09)
Tongue coating	L*a*b	TB-MEAN	0.03 (0.01)	0.03 (0.01)	0.03 (0.01)
		TC-L	79.24 (76.15–81.91)	78.62 (75.88–81.64)	78.43 (74.74–80.64)
		TC-a	10.16 (8.47–12.72)	9.81 (8.16–12.6)	10.62 (8.78–12.73)
	Tongue coating index	TC-b	4.02 (2.18)	4.12 (1.99)	3.64 (2.76)
		perAll	0.54 (0.42–0.71)	0.52 (0.45–0.74)	0.5 (0.41–0.64)
		perPart	1.1 (1.04–1.27)	1.12 (1.03–1.36)	1.12 (1.04–1.37)
	Texture index	TC-CON	111.92 (82.71–149.38)	120.44 (90.91–155.21)	102.62 (75.39–137.96)
		TC-ENT	1.32 (1.25–1.38)	1.33 (1.27–1.39)	1.3 (1.23–1.37)
		TC-ASM	0.06 (0.05–0.07)	0.06 (0.05–0.07)	0.06 (0.05–0.07)
		TC-MEAN	0.03 (0.03–0.04)	0.03 (0.03–0.04)	0.03 (0.03–0.04)

Note: * significantly different from stage I; # significantly different from stage II + III. The *t*-test or Mann-Whitney U test was used. $P < 0.05$, the difference was statistically significant.

Table 8
Logistic analysis of tongue image characteristics in different pathological stages

Stages	Project	B	OR	95% CI.		P
				Lower limit	Upper limit	
Reference category: Stage I						
Stage IV	Gender	0.297	1.346	0.603	3.001	0.468
	Age	0.004	1.004	0.967	1.042	0.830
	Smoking history	0.846	2.331	0.854	6.360	0.099
	Operation	-2.926	0.054	0.021	0.136	0.000
	Course of disease	0.049	1.051	1.031	1.071	0.000
	Pathological type	-0.121	0.886	0.255	3.082	0.850
	TB-a	0.151	1.163	1.046	1.294	0.005
	TB-b	-0.306	0.737	0.611	0.887	0.001
Reference category: II + III						
Stage IV	Gender	-0.434	0.648	0.266	1.577	0.339
	Age	-0.020	0.980	0.938	1.024	0.363
	Smoking history	-0.096	0.908	0.364	2.269	0.837
	Operation	-0.943	0.389	0.175	0.867	0.021
	Course of disease	0.032	1.033	1.009	1.058	0.008
	Pathological type	-0.595	0.551	0.220	1.379	0.203
	TB-b	-0.323	0.724	0.594	0.882	0.001
	TC-a	0.158	1.171	1.016	1.349	0.029

Note: The dependent variable was a pathological stage (1 = stage I group, 2 = II + III stage group, 3 = stage IV group). The control variables included the course of the disease, age, sex (1 = female, 2 = male), smoking history (0 = yes, 1 = none), pathological classification (1 = adenocarcinoma, 2 = squamous cell carcinoma), and surgery (0 = no operation, 1 = surgery). Independent variables included TB-L, TB-a, TB-b, TC-L, TC-a, TC-b, TBASM, and perAll. There was no collinearity problem in any variables ($VIF < 10$). Therefore, only the tongue image indexes that can be entered into the regression equation are included in the table ($P < 0.05$).

The results in Table 8 show that after controlling for the influence of sex, age, smoking history, pathological classification, surgery, and course of the disease, taking stage I as the reference category, no characteristic tongue image index in stage II + III group entered the equation ($P > 0.05$); TB-a and TB-b in the stage IV group were entered into the equation ($P < 0.05$). The OR value of TB-a was greater than 1 (OR = 1.163); TB-a was a risk factor for stage IV disease, meaning that TB-a increased, and the risk of stage IV disease increased. The OR value of TB-b was less than 1 (OR = 0.737); that is, TB-b is the protective factor for the occurrence of stage IV, and the increase in TB-b reduces the risk of stage IV. the OR value of TB-b in stage IV group was less than 1 (OR = 0.724); that is, TB-b was a protective factor for the occurrence of Taking II + III as the reference category, stage IV, and the OR value of TC-a was greater than 1 (OR = 1.171); that is, as TC-a increased, the risk of occurrence of stage IV increased.

These results show that after controlling for the effects of sex, age, smoking history, pathological classification, surgery, and disease course, the tongue image indices of stage IV NSCLC were lower than those of stage I TB-b and TB-a. Compared with stage II + III, TB-b is lower, TC-a is increased, and the risk of stage IV is increased. Conversely, TB-b is decreased, TB-a is increased, and the risk of stage IV is increased compared with stage I. Therefore, an increase in TC-a indicates that the red component of the tongue is increased or the tongue coating becomes thinner, which causes the red component of the tongue to appear. In conclusion, compared with patients with stage I and II + III NSCLC, the red component of the tongue in patients with stage IV NSCLC is decreased, and the blue component is increased, showing the characteristics of a bruising tongue.

4. Discussion

NSCLC is all epithelial cancer except SCLC. All types of NSCLC are likely to occur. The most common types of NSCLC are adenocarcinomas, squamous cell carcinomas, and large cell carcinomas. The etiology and pathogenesis of tumors are complex, and their etiology remains unknown. The top risk factors for lung cancer are age, smoking history, past cancer history, family history, and occupational exposure [16].

The results showed that compared with the elderly control group, the tongue body and tongue coating brightness of NSCLC patients increased, the red component decreased, the tongue coating thickened, and the yellow component increased. In addition, the texture of the tongue coating was more delicate, showing a tendency for the thick and greasy coating to change. 1235 tongue images of NSCLC were compared with those of 163 healthy controls. The results showed that the brightness of the NSCLC tongue increased, the red component decreased, the tongue coating thickened, and the yellow component increased. This conclusion is similar to those of previous studies.

Preliminary findings show that a thick tongue with reduced brightness distinguishes a tongue image of NSCLC from that of a healthy tongue. A binary logistic stepwise regression was used to control for gender and age since there was a significant difference in the age distribution between the NSCLC group and the healthy control group ($P < 0.05$) to exclude the influence of age and gender on the tongue image. The results showed that the three variables that could enter the regression equation were all tongue-related indicators. According to the team's previous study, perAll had a higher diagnostic value for a thick tongue, with a higher value indicating a thicker tongue. Logistic regression results also showed that a thick tongue was a risk factor for NSCLC, and the intensity of the effect was higher, indicating that a thicker tongue indicated an increased likelihood of NSCLC.

Generally, the development of tumor disease from stage I to stage IV is a gradual process from excessive pathogenic factors to positive deficiency. However, because of chronic diseases, phlegm and blood stasis are often produced. In the later clinical stage, the increase in TCM deficiency syndrome and mixed syndromes, and the appearance of the tongue changes from pale to dark and even bruised. The results of this experiment showed that there was no significant difference between the phase I group and the stage II + III index. The stage IV group showed a decrease in TB-b compared to the stage I and II + III groups. A decrease in TB-b indicates an increase in the blue component of the tongue. When the blue component of the tongue increased, the tongue became greener, and the brightness decreased. In the binary logistic regression analysis, after eliminating the influence of other confounding factors, TB-b in stage IV was positively correlated with stages I and II + III, which also showed that the blue component of the tongue image in stage IV increased. Comprehensively showing that patients in the stage IV group are bluer than those in stage I and II + III. The results showed that the change in tongue image in NSCLC patients was not significant from the beginning of stage I to the deepening of tongue color and the appearance of blue and purple tongues with the progression of the disease. This change was not obvious in the comparison between stage II and III and stage I patients. Compared with the previous three stages, patients in stage IV changed significantly. It also reflects that with the course of NSCLC, phlegm and blood stasis intermingled, and blood stasis appeared in the tongue. A clinical research report showed that NSCLC was mostly a blue-purple tongue, and the degree of bluish-purple coloration was aggravated with the progression of the disease [25]. Li Xiaojuan believed in the research on the pathogenesis of lung cancer in TCM that there are more patients with Qi deficiency and blood stasis syndrome in the middle and late stages of lung cancer, and they are accompanied by coagulation dysfunction [26]. The change in the coagulation index is related to tumor staging. In this study, tongue images of patients with NSCLC

at different stages were described using objective tongue image indicators. The results showed that the tongue color of patients with advanced lung cancer was bluish and purple in the early and middle stages, consistent with previous research. It is proposed that tongue image features can reflect the characteristics of different stages of NSCLC, especially the tongue features of stage IV, which also means that tongue image features can be used as a reference for judging the course of NSCLC.

5. Conclusion

The results of this study show that tongue imaging features can provide an objective basis for the diagnosis and efficacy evaluation of NSCLC and can also provide new ideas and methods for the diagnosis and treatment of NSCLC using a combination of traditional Chinese and Western Medicine. The construction of this study was based on a clinical cross-section and belongs to a retrospective case-control design, which is a more commonly used research method for risk prediction models. But models constructed on the basis of disease outcome are not predictive models in the strict sense, while controlled studies have certain limitations, such as the inability to specify risk factors for the outcome and the possibility of bias in the selection of study subjects, etc., which to a certain extent have an impact on the accuracy and reliability of the study.

However, in the future, we will further expand the sample size for research because the clinical conditions are limited, the number of samples is too small, it is based on a cross-sectional study, and there is not enough observation time for continuous observation of pathological changes in samples. Moreover, this study shows that tongue coating changes have important implications in the progression of NSCLC; therefore, further studies will be conducted in the future.

Author contributions

Ling-zhi Zeng and Ji Cui contributed equally to this work. Ling-zhi Zeng designed the study and drafted the manuscript. Ji Cui was responsible for preprocessing the data and checking the results. Tao Jiang and Hai-dan Liu enrolled study subjects and collected data. Ji Cui and Li-ping Tu provided support on data analysis and interpretation. Ya-bin Gong and Ling Xu offered suggestions. Ji Cui and Jia-tuo Xu are the corresponding authors. All authors have reviewed and approved the final manuscript.

Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Data availability statement

The datasets generated and analyzed during the current study are not publicly available due to the confidentiality of the data, which is an important component of the National Key Technology R&D Program of the 13th five-year plan (No. 2017YFC1703301) in China. However, the datasets are available from the corresponding author upon reasonable request.

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