Tongue texture may contribute to the assessment of malignant risk of thyroid nodules

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Abstract. In the present study, it was aimed to evaluate whether there is an objective tongue image indicator that could be used to evaluate malignant risk of thyroid nodules through a cross sectional study. From December 2018 to December 2020, the TFDA-1 digital tongue-face diagnostic instrument was used to collect the tongue images. TDAS 2.0 software was used for tongue image analysis. A standardized database was constructed by combining patient physical examination results and tongue image analysis results. The relationship between tongue image index and TI-RADS classification of thyroid nodules was tested. A total of 5,900 cases were collected and 4,615 cases were included in the present study after excluding 154 cases due to incomplete information, 1,221 cases with thyroid nodules were separated into 417 cases TI-RADS 2 group, 693 cases in TI-RADS 3 group and 111 cases in TI-RADS 4 group. Without considering confounding factors, tongue image indexes zhiCon, zhiASM, zhiENT, zhiMEAN, zhiClrB, zhiClrR, zhiClrG, zhiClrI, zhiClrL and zhiClrY were significantly different among the three groups (P<0.05). Excluding the influence of age, sex, body mass index, smoking and drinking, the results of one-way variance linear trend analysis showed that the values of zhiCon, zhiENT and zhiMEAN increased with the increasing TI-RADS category, while the values of zhiASM decreased with the increase of TI-RADS category. Tongue texture index may be helpful for differentiating the benign and malignant of thyroid nodules.

Introduction

Thyroid nodule is usually benign tumor that is commonly noticed in clinical practice and often in incidental findings while doing ultrasound. The detection rate can be as high as 68% (1,2), of which only 5% of thyroid nodules are malignant (3,4). A recent study reported that in 2020 ~580,000 patients were diagnosed with thyroid cancer globally, accounting for 3.0% out of all new cancers in a year, with 43,000 patients succumbing due to thyroid cancer (5). Ultrasound, a non-invasive and inexpensive medical examination, is commonly used to screen for thyroid diseases (6-9). The Thyroid Imaging Reporting and Data System (TI-RADS) is used in clinical practice for reporting and differentiating benign and malignant thyroid nodules based on ultrasound imaging features.

Tongue diagnosis has thousand-years of history in China, which is an important part of the diagnostic method of traditional Chinese medicine. Empirical clinical practice and academic research had proved that the occurrence and development of disease is often accompanied with the changes of tongue, which is indicative of the severity of the disease (10-14). For example, Chen *et al* (15) found that the tongue image parameter S value is larger, the RGB color component value is smaller among hypertensive patients with cracked tongue compared with normal group. Qian *et al* (16) found that the RGB value, H value and V value of tongue color and moss color in gastric tumor patients were higher than those in the normal group, while the S value and H value of tongue color were lower than those in the normal group.

Tongue image observation may provide useful information of the features of thyroid nodule malignancy. The present study evaluated the relationship between the parameters of patients' tongue images and TI-RADS classification of thyroid nodule to determine the effectiveness of using tongue images in differentiating the benign and malignant thyroid nodules.

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Key words: thyroid nodules, tongue image features, benign and malignant judgment

Materials and methods

Source of cases. Patients who underwent physical examination and were diagnosed with thyroid nodule in the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (Guangzhou, China) from December 2018 to December 2020 were included. The studies involving human participants were reviewed and approved (approval no. 2018KL-050) by The Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (Guangzhou, China). Written informed consent was provided by all the patients/participants to participate in the present study. The acquisition instrument that was used to collect tongue images, was the TFDA-1 digital tongue-face diagnostic instrument developed by Shanghai University of Traditional Chinese Medicine (Fig. 1), which mainly includes Charge coupled Device equipment, LED light source, light mask, and curved reflective mask. The color temperature of LED lamp is 5,000 K, and the color rendering index is 97. The camera settings were as follows: M mode, shutter 1/125, aperture F6.3, ISO 200, central key metering. The collection time was between 8:00 and 12:00 am, Monday to Friday, from December 2018 to December 2020. The risk of malignancy of thyroid nodules was determined using TI-RADS criteria based on the American College of Radiology (ACR) Thyroid Imaging Reporting and Data System published in 2017 (2). Diagnostic criteria were as follows: Inclusion criteria for patients with thyroid nodules included: i) Age (≥18 and ≤75 years); ii) healthy people who did not suffer from any acute or chronic diseases in the prior 3 months before entering the study, and have confirmed thyroid nodules with risk of malignancy determined by the TI-RADS classification in the physical examination report; iii) patient can complete tongue image acquisition independently; and iv) voluntarily consent to tongue image acquisition and analysis and sign the informed consent. Exclusion criteria included: i) Eating colored food and drugs within 2 h before tongue image acquisition due to potential impact on the tongue image judgment of reviewers; ii) Tthe basic information (sex, age, height, weight) and experimental data were incomplete; (ii) suffering from serious heart, brain, kidney diseases or other serious diseases; iv) patients suffering severe symptoms of depression and anxiety; v) patients with hypertension, diabetes, anemia and other diseases affecting the tongue image accuracy: and vi) pregnant and lactating women.

Tongue image acquisition method: i) Researchers disinfected the outer ring and inner ring of the tongue surface examination instrument with 75% alcohol. At the same time, the light source and parameters of the instrument were checked to ensure it meeting the acquisition requirements. After the physical examination patient arrived at the clinic, relevant communication was conducted to eliminate the patient's concerns about collection, and relevant matters needing attention were explained. Patients were then invited to participate in the collection and informed consent was provided to them.

ii) After a 5-10 min resting, patients were asked to wear medical earphones, and slightly forwarded their body, and put their mandible on the tongue diagnosis instrument (jaw does not exceed the built-in damper), the researchers opened the built-in light and ensured that no mist covered the camera and patients' forehead was not covered by hair. Then the patient was instructed to extend the tongue outside of the mouth, and the tongue body was kept relaxed with the tip of the tongue pointing down. The surface of the tongue was intact, flattened, and relaxed, and tongue images were collected.

Tongue image segmentation and analysis. The tongue diagnosis analysis system (Tongue Diagnosis Analysis System, TDAS version 2.0) developed by the Intelligent Diagnostic Technology Research Laboratory of Shanghai University of Traditional Chinese Medicine completed the segmentation and analysis of the tongue image. TDAS 2.0 system can be used calculate the component values of tongue substance and tongue coating in RGB, HIS, Lab and YCrCb color Spaces, as well as Contrast (CON) and Entropy (ENT), Angular Second Moment (ASM) and MEAN (MEAN), and two coating thickness indexes, perAll and perPart.

RGB. RGB color space, based on the three basic colors R(Red), G(Green), B(Blue), superposition in different degrees to produce rich and extensive colors, also known as the three primary color mode. It is a unit length cube to represent color, eight vertices are eight common colors (black, blue, green, red, cyan, purple, yellow and white), generally put black at the origin of the three-dimensional cartesian coordinate system, the three axes are red, blue and green three colors. The value of each parameter ranges from: R: 0-255. G: 0-255; B: 0-255.

Lab. It indicates the Lab color space. L (lightness) indicates the color space from pure black to pure white, and the value range is 0-100. The value of 0 represents pure black and 100 represents pure white. A and B represent the green-red axis and the blue-yellow axis respectively, and their value ranges from 127 to minus (-)128. Lab IS a device-independent, physiology-based color system that uses digital methods to describe human visual perception.

YCrCb. YUV orthogonal color space, Y represents brightness, U and V represent chroma, which is used to describe the image color and saturation for specified pixels of color. 'Brightness' is established through the RGB input signal. 'Chroma' is defined by two aspects of color-hue and saturation-, denoted by Cr and Cb, respectively. Cr reflects the difference between the red part of RGB input signal and the brightness value of RGB signal. Cb reflects the difference between the blue part of RGB input signal and the brightness value of RGB signal.

HIS. Cognitive color space. Starting from human visual system, colors are described by H (hue), S (color saturation) and I (brightness). Color model describes color characteristics by H, S and I, where H defines the wavelength of color, also known as hue. S represents the depth of the color, known as saturation; I represents intensity or brightness.

Contrast (CON). It reflects the sharpness and depth of texture grooves of an image. The deeper the texture furrow, the greater the contrast and the clearer the visual effect. On the contrary, the smaller the contrast, the shallower the furrow, and the image is blurred.

$$CON = \sum_i i^2 p(i)$$

Angular Second Moment (ASM). ASM reflects the uniformity of image gray distribution and texture thickness. If all values are equal, then ASM value is small. Conversely, if some of these values are large and others are small, then ASM value is large. Large ASM values indicate a more uniform and regularly varying texture pattern.

$$ASM = \sum_i [p(i)]^2$$

Entropy (ENT). ENT is a measure of the amount of information in an image. Texture information also belongs to the

Table I. TI-RADS classification by sex.

Classification		Sex		c[2]	P-value
		Male (percentage)	Female (percentage)		
Classification of thyroid nodules	TI-RADS 2	176 (42.2%)	241 (57.8%)	4.053	0.132
	TI-RADS 3	264 (38.1%)	429 (61.9%)		
	TI-RADS 4	36 (32.4%)	75 (67.6%)		
Total		476 (39.0%)	745 (61.0%)		

TI-RADS, Thyroid Imaging Reporting and Data System.

Figure 1. Thyroid Imaging Reporting and Data System-1 tongue instrument.

information of an image and is a random measure. When all elements in the co-occurrence matrix have the largest randomness and all values in the spatial co-occurrence matrix are almost equal, and the distributions of elements in the co-occurrence matrix are dispersed, the entropy is large. It represents the non-uniformity or complexity of the texture of the image.

$$ENT = -\sum_i p(i)\log p(i)$$

Mean: indicates the average gray value of the image.

$$MEAN = \frac{1}{m}\sum_i ip(i)$$

PerAll is the ratio of tongue coating area to total tongue area (perAll=tongue coating area/total tongue area). PerPart is the ratio of coated tongue area to uncoated tongue area (perPart=coated tongue area/uncoated tongue area).

Data cleaning. Demographic data of patients, medical and clinical characteristics were extracted from the databases of Physical examination Center of Chengdu university of traditional Chinese medicine hospital and collated in Microsoft Excel spreadsheet, which were further merged with the tongue image analysis results using TDAS 2.0 System.

Statistical analysis. The statistical software used in the present study was SPSS 24.0 (IBM Corp.) and P<0.05 was considered to indicate a statistically significant difference. Data was summarized by the mean ± standard deviation and median (interquartile range) according to the normality of the data distribution. For group comparisons, independent sample t-test (unpaired) or non-parametric test (Mann-Whitney U test) was used according to the data distribution. Chi-square (χ^2) test was used to analyze the difference of constituent ratio between different groups. For the analysis of influencing factors, logistic regression was selected for binary outcome variables and linear regression was selected for continuous outcome variables. One-way variance linear trend analysis was used for trend analysis among multiple groups.

Results

A total of 5,900 cases were collected in the present study; 152 cases were excluded due to lack of information, leaving 5,748 cases included in the final analysis. According to the inclusion and exclusion criteria, 1,221 patients with thyroid nodules were screened (Fig. 2), including 476 males and 745 females (Table I), with a median age of 45 (range, 32-56) years. Patients with thyroid nodules were divided into three groups according to TI-RADS classification. There were 417 cases in TI-RADS 2 group, 693 cases in TI-RADS 3 group, and 111 cases in the TI-RADS 4 group (including TI-RADS 4A, TI-RADS 4B, TI-RADS 4C and TI-RADS 5). For patients with two or more thyroid nodules, classification was made according to the nodule with the highest risk; for example, if a patient had both TI-RADS 2 and TI-RADS 3 nodules, he/she were classified into TI-RADS Category 3 group.

The distribution of all of the tongue image indexes in the present study were skewed, and the tongue image indexes of different TI-RADS classification were compared by non-parametric test (Table II). According to the comparison

Table II. Tongue image feature table of different TI-RADS categories of thyroid nodules (without considering confounding factors).

Tongue image index	Classification of thyroid nodules			c^2	P-value
	TI-RADS 2	TI-RADS 3	TI-RADS 4		
zhiR	0.448 (0.437~0.457)	0.448 (0.44~0.458)	0.447 (0.438~0.459)	2.948	0.229
zhiG	0.275 (0.269~0.281)	0.275 (0.269~0.28)	0.275 (0.268~0.282)	0.845	0.656
taiR	0.416 (0.406~0.427)	0.417 (0.408~0.426)	0.417 (0.409~0.425)	0.513	0.774
taiG	0.293 (0.287~0.298)	0.293 (0.289~0.298)	0.293 (0.287~0.298)	0.549	0.76
perAll	0.368 (0.29~0.429)	0.37 (0.302~0.424)	0.376 (0.307~0.437)	0.285	0.867
perPart	0.682 (0.603~0.877)	0.696 (0.595~0.87)	0.676 (0.592~0.8)	0.313	0.855
zhiCon	87.995 (72.517~111.77)	92.707 (73.414~117.174)	100.034 (79.859~116.422)	7.178	0.028
taiCon	113.679 (88.826~145.044)	117.929 (91.615~152.239)	115.5 (87.571~140.689)	5.056	0.08
zhiASM	0.066 (0.058~0.075)	0.065 (0.057~0.074)	0.063 (0.057~0.07)	8.179	0.017
zhiENT	1.257 (1.21~1.311)	1.267 (1.214~1.323)	1.286 (1.229~1.323)	7.347	0.025
zhiMEAN	0.029 (0.026~0.033)	0.03 (0.027~0.034)	0.031 (0.028~0.034)	7.706	0.021
taiASM	0.057 (0.051~0.066)	0.056 (0.05~0.064)	0.058 (0.051~0.066)	4.098	0.129
taiENT	1.314 (1.258~1.371)	1.324 (1.266~1.378)	1.316 (1.252~1.361)	4.637	0.098
taiMEAN	0.034 (0.03~0.038)	0.034 (0.03~0.039)	0.034 (0.029~0.037)	4.711	0.095
zhiClrB	99 (94~104)	97 (92~102)	98 (93~103)	12.81	0.002
zhiClrR	159 (155~163)	157.5 (153~161)	159 (155~163)	17.27	<0.001
zhiClrG	97 (92~102)	97 (91~101)	97 (92~103)	7.241	0.027
taiClrR	149 (141~155)	148 (140~155)	150 (141~154)	0.414	0.813
taiClrG	105 (96~113)	105 (95~112)	105 (96~113)	0.323	0.851
taiClrB	104 (95.25~112)	104 (94~111)	104 (96~111)	1.138	0.566
zhiClrH	355.889 (1.689~358.045)	355.142 (1.718~357.763)	353.413 (0.91~357.581)	2.59	0.274
zhiClrI	118 (114~122)	117 (112~121)	118 (114~122)	13.036	0.001
zhiClrS	0.181 (0.164~0.195)	0.183 (0.169~0.198)	0.181 (0.165~0.195)	5.069	0.079
taiClrH	5.436 (1.369~356.802)	5.076 (1.504~356.329)	4.044 (2.156~354.564)	0.905	0.636
taiClrI	120 (111~126)	119 (110~126)	120 (110~125)	0.597	0.742
taiClrS	0.133 (0.115~0.149)	0.133 (0.118~0.152)	0.135 (0.125~0.148)	2.057	0.358
zhiClrL	48.151 (46.541~49.749)	47.746 (45.812~49.253)	48.161 (46.515~49.658)	11.052	0.004
zhiClrLa	24.931 (23.005~26.711)	24.666 (23.203~26.314)	24.568 (22.939~26.793)	1.06	0.589
zhiClrLb	9.803 (8.384~11.159)	10.037 (8.55~11.36)	10.233 (8.972~11.504)	3.522	0.172
taiClrL	49.119 (45.334~51.661)	48.676 (45.115~51.572)	49.096 (45.314~51.497)	0.388	0.824
taiClrLa	17.19 (15.498~19.087)	17.232 (15.651~18.638)	17.452 (16.059~18.9)	0.918	0.632
taiClrLb	7.212 (6.146~8.542)	7.378 (6.169~8.833)	7.864 (6.416~8.99)	3.776	0.151
zhiClrY	115.583 (111.976~119.224)	114.66 (110.483~118.151)	115.665 (111.997~119.063)	10.96	0.004
zhiClrCr	154.715 (152.75~156.335)	154.435 (153.038~156.049)	154.424 (152.821~156.181)	0.835	0.659
zhiClrCb	119.54 (118.521~120.573)	119.535 (118.371~120.43)	119.255 (118.223~120.276)	2.935	0.231
taiClrY	117.825 (109.758~123.442)	116.966 (109.283~123.221)	117.9 (109.648~122.89)	0.407	0.816
taiClrCr	146.958 (145.426~148.699)	147.101 (145.64~148.418)	147.243 (145.854~148.561)	1.009	0.604
taiClrCb	121.335 (120.309~122.229)	121.322 (120.166~122.214)	120.891 (120.018~122.066)	4.196	0.123

TI-RADS, Thyroid Imaging Reporting and Data System.

results, the tongue image indexes zhiCon, zhiASM, zhiENT, zhiMEAN, zhiClrB, zhiClrR, zhiClrG, zhiClrI, zhiClrL and zhiClrY were significantly different among the three groups ($P<0.05$).

Additional analysis found that age, sex, body mass index (BMI), smoking and drinking also affected the prevalence of thyroid nodules and tongue images. Results from analysis using multiple linear regression adjusting for age, sex, BMI, smoking and drinking dealt as confounding factors, for index with statistical differences are shown in Table III.

In the multiple linear regression analysis adjusting for age, sex, BMI, smoking history and Tongue image indexes zhiCon, zhiASM, zhiENT and zhiMEAN were significantly different between patients in TI-RADS 4 and TI-RADS 2 category ($P<0.05$). Compared with TI-RADS 2 category, patients in TI-RADS 3 category had different tongue image indexes of

Table III. Multiple linear regression of tongue image indicators with statistical differences in Table II (with TI-RADS 2 as the reference).

	Age	Body mass Index	Sex		Smoking		Drinking		TI-RADS		
			Male	Female	Yes	No	Yes	No	2	3	4
Tongue image index	B/P	B/P	B	B/P	B	B/P	B	B/P	B	B/P	B/P
zhiCon	0.175/0.008	-0.088/0.636	0	-6.274/0.007	0	-5.195/0.071	0	-5.176/0.056	0	2.5/0.219	8.183/0.016
zhiASM	<0.001/0.07	<0.001/0.97	0	0.003/0.098	0	0.001/0.781	0	0.003/0.081	0	-0.002/0.137	-0.005/0.035
zhiENT	<0.001/0.034	<0.001/0.704	0	-0.015/0.015	0	-0.006/0.415	0	-0.015/0.029	0	0.007/0.165	0.022/0.015
zhiMEAN	<0.001/0.015	<0.001/0.526	0	-0.001/0.012	0	-0.001/0.077	0	-0.001/0.031	0	<0.001/0.214	0.001/0.007
zhiClrB	-0.081<0.001	0.095/0.085	0	-0.173/0.801	0	-1.726/0.042	0	-1.771/0.027	0	-1.367/0.023	-0.429/0.669
zhiClrR	-0.088/<0.001	0.01/0.856	0	1.571/0.022	0	0.12/0.888	0	-0.703/0.38	0	-1.186/0.049	-0.199/0.843
zhiClrG	-0.032/0.09	0.041/0.454	0	2.375/<0.001	0	-1.312/0.117	0	-1.449/0.066	0	-1.211/0.041	-0.018/0.986
zhiClrI	-0.068/<0.001	0.051/0.327	0	1.249/0.053	0	-0.966/0.227	0	-1.316/0.08	0	-1.24/0.028	-0.181/0.849
zhiClrL	-0.021/0.005	0.014/0.508	0	0.75/0.003	0	-0.335/0.292	0	-0.479/0.11	0	-0.478/0.034	-0.036/0.923
zhiClrY	-0.045/0.005	0.033/0.472	0	1.567/0.006	0	-0.798/0.258	0	-1.096/0.099	0	-1.081/0.03	-0.102/0.903

TI-RADS, Thyroid Imaging Reporting and Data System.

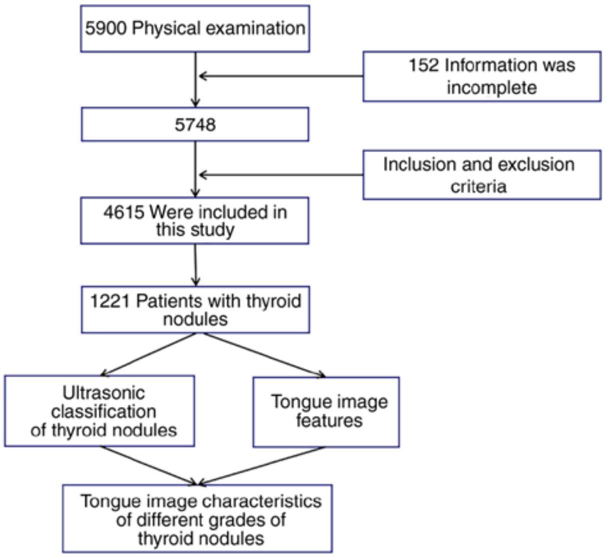

Figure 2. Flow chart of the present study.

zhiClrB, zhiClrR, zhiClrG, zhiClrI, zhiClrL, and zhiClrY ($P<0.05$). Specifically, compared with TI-RADS 2, the values of zhiCon, zhiENT and zhiMEAN in TI-RADS 4 increased by 8.183, 0.022 and 0.001 respectively, while the values of zhiASM decreased by 0.005. Compared with TI-RADS 2, the values of TI-RADS 3 in tongue image index zhiClrB, zhiClrR, zhiClrG, zhiClrI, zhiClrL and zhiClrY are 0.429, 0.199, 0.018, 0.181, 0.036 and 0.102, respectively.

In order to further explore the trend of tongue image indexes with different TI-RADS classification, one-way variance linear trend analysis was used to examine the linear trend of the aforementioned indexes observed in Table III, with the results shown in Table IV.

According to Table IV, there was a linear trend in term of tongue image indexes zhiCon, zhiENT, zhiASM and zhiMEAN across different TI-RADS categories ($P\leq0.05$), while no trend was observed for other tongue image indexes ($P>0.05$). The trend in zhiCon, zhiENT, zhiASM and zhiMEAN suggests that zhiCon, zhiENT and zhiMEAN values increase and zhiASM decrease with the increase of TI-RADS classification (Fig. 3).

In Table V and Fig. 3, the linear trend of tongue image indexes zhiCon, zhiENT, zhiASM and zhiMEAN across the groups is demonstrated. In Fig. 4, with the increase of TI-RADS categories, the tongue surface becomes more granular, and the tongue texture becomes rougher.

Discussion

The present study revealed that TI-RADS classification was positively associated with tongue image indexes zhiCon, zhiENT and zhiMEAN and negatively associated with tongue image index zhiASM. Existing research results have revealed that zhiCon, zhiENT and zhiMEAN increase as zhiASM decreases. The rougher the tongue texture, the more delicate the opposite (17). Although the TI-RADS categories developed in different countries and regions differ in the risk assessment of malignant transformation of thyroid nodules (2,18-23),

Table IV. One-way linear trend analysis of variance for different types of tongue image indicators in TI-RADS.

			95% confidence interval			
Tongue image index	TI-RADS	Mean ± standard deviation	Lower	Upper	F	P-value
zhiCon	2	93.38±31.56	90.34	96.42	4.516	0.034
	3	96.85±32.72	94.44	99.29		
	4	100.7±31.85	94.71	106.69		
zhiENT	2	1.255±0.09	1.247	1.264	4.806	0.029
	3	1.264±0.08	1.258	1.27		
	4	1.275±0.077	1.26	1.289		
zhiASM	2	0.069±0.031	0.066	0.072	3.848	0.05
	3	0.067±0.013	0.066	0.068		
	4	0.065±0.012	0.062	0.067		
zhiMEAN	2	0.03±0.005	0.029	0.03	5.874	0.016
	3	0.03±0.005	0.03	0.031		
	4	0.031±0.005	0.03	0.032		
zhiClrB	2	98.41±9.741	97.47	99.35	0.399	0.528
	3	96.45±9.585	95.74	97.17		
	4	97.77±8.093	96.24	99.29		
zhiClrR	2	157.93±9.13	157.05	158.81	0.033	0.855
	3	156.15±9.95	155.4	156.89		
	4	157.75±7.74	156.29	159.2		
zhiClrG	2	97.11±9.37	96.21	98.01	0.006	0.939
	3	95.76±9.41	95.05	96.46		
	4	97.19±8.14	95.66	98.72		
zhiClrI	2	117.48±8.84	116.63	118.33	0.052	0.82
	3	115.79±9.14	115.11	116.47		
	4	117.26±7.39	115.87	118.65		
zhiClrL	2	47.912±3.526	47.572	48.251	0.002	0.963
	3	47.309±3.629	47.039	47.58		
	4	47.894±2.916	47.345	48.442		
zhiClrY	2	115.147±7.588	114.417	115.878	0.007	0.932
	3	113.79±8.176	113.181	114.4		
	4	115.076±7.856	113.867	116.284		

TI-RADS, Thyroid Imaging Reporting and Data System.

there is a common trend: The risk of malignant transformation increases with the increasing TI-RADS categories (Table VI). Therefore, it was hypothesized that the factors that lead to the change of tongue texture may also be the factors that lead to the malignant degeneration of thyroid nodules.

Tongue texture is a comprehensive expression of tongue coating, filamentous papilla, fungoides papilla, tongue crack and so forth. Inflammation is a common cause of tongue disease (24). Existing previous studies have discovered that the inflammation of filamentous papilla can cause its atrophy, the thinning of epithelium, fiery red on the back of the tongue, and shallow furrow fissure (A special tongue texture) (25). Inflammation of fungal papilla can lead to its congestion, redness and swelling (24), and forming the granular texture features on the back of tongue. The aforementioned phenomena could lead into making the tongue texture rougher. The factors leading to the filamentous and fungal papillary inflammation of tongue may be attributable to anemia, vitamin deficiency, antibiotic abuse, endocrine disorders, malnutrition, and other health conditions (24). Some of these factors are clearly associated with thyroid diseases, but some are controversial. A previous study by Refaat (26) revealed that the incidence of anemia in women with thyroid disease was significantly higher than that in women without thyroid disease (44 vs. 14.3%). At the same time, it was found that compared with the normal group, the abnormal thyroid group had a significant decrease in red blood cell count, hemoglobin, hematocrit, serum iron and serum ferritin. Ren *et al* (27,28) found that the prevalence of anemia in patients with thyroid cancer is 36.7% (population average 24.8%). The vitamin deficiency in patients with thyroid diseases is mainly characterized by the deficiency of vitamins B6 and D. Jia *et al* (29) found that low vitamin B6 levels were associated with presence of thyroid nodules. Hu and Rayman (30) found that patients with Hashimoto's

Table V. Examples of linear trend of tongue image index zhiCon, zhiENT, zhiASM and zhiMEAN.

	Tongue image index			
TI-RADS classification	zhiCon	zhiASM	zhiENT	zhiMEAN
2	63.85	0.079	1.186	0.025
3	117.2	0.055	1.329	0.034
4a	159.128	0.05	1.386	0.039

TI-RADS, Thyroid Imaging Reporting and Data System.

Table VI. Comparison of malignant change risk in different TI-RADS classification.

	Risk of malignancy in different TI-RADS classification (%)					
Author/(Refs.) (year)	TI-RADS 1	TI-RADS 2	TI-RADS 3	TI-RADS 4	TI-RADS 5	TI-RADS 6
Tessler FN, *et al* (2) (2017)	0	<2%	<5%	5-20%	>20%	-
Park JY, *et al* (18) (2009)	0-7%	8-23%	24-50%	51-90%	91-100%	-
Kwak JY, *et al* (19) (2011)	0	0	2.0-2.8%	3.6-91.9%	88.7-97.9%	-
Russ G, *et al* (21) (2017)	0	≅0	2-4%	6-17%	26-87%	-
Superficial Organ and Vascular Ultrasound Group, Society of Ultrasound in Medicine, Chinese Medical Association (22) (2021)	0	0	<2%	2-90%	>90%	100%
Horvath E, *et al* (23) (2009)	0	0	<5%	5-80%	>80%	100%

TI-RADS, Thyroid Imaging Reporting and Data System.

thyroiditis had lower vitamin D levels compared with those who did not have this disease. Nutritional factors including iodine, iron and selenium have also been shown to be associated with thyroid disease. For example, chronic exposure to excess iodine intake can induce autoimmune thyroiditis and iron deficiency can impair thyroid metabolism (30). Another study found that low selenium and low vitamin D levels may increase the risk of developing autoimmune thyroid disease, although these data are not conclusive and more studies are needed to verify this result (31).

Tongue crack (Fissured Tongue) may be caused by the combination of innate factors and acquired factors, the acquired factors mainly included geographical environment and dietary nutrition. Existing studies have found increased rates of split tongue in men [60.7% (female 39.3%)] as well as patients with diabetes [42.1% (healthy individual, 22.5%)] functional dyspepsia [78.9%, (healthy individual 3.2-27.2%)] and psoriasis [36%, (healthy individual, 20%)] (32-35). In addition, previous studies have demonstrated that male individuals with diabetes exhibit a significantly higher risk of developing thyroid nodules (36,37). One possible reason for the higher incidence of cracked tongue in men than in women is the higher smoking rate (35), as smoking is an important risk factor for thyroid nodule (37). The reasons for the higher incidence of cracked tongues in patients with diabetes than in those without diabetes are more complex. It could be due to inadequate blood glucose control, immunological changes, microcirculatory alternation with reduced blood flow, xerostomia and alteration in salivary flow and composition (35). The association between type 2 diabetes mellitus (T2DM) and thyroid nodules has been purportedly attributed to abnormal glucose and lipid metabolism in patients with diabetes (38,39). Zhang *et al* (38) found that compared with patients with benign nodules, T2DM patients with malignant thyroid nodules had lower serum HDL-C levels and higher levels of IGF-1, HbA1c and TgAb. Serum levels of HDL-C, IGF-1, HbA1c and TgAb were also found to be correlated with the degree of malignancy of thyroid nodules (TI-RADS score) in patients with T2DM.

At present, the most effective method for distinguishing benign and malignant thyroid nodules is fine-needle aspiration (FNA); however, most nodules are benign, and the use of FNA may not be a safe option for initial screening or testing (2). Although TI-RADS gives the classification of nodules, the accuracy of judgment (such as the risk of malignant transformation of TI-RADS 3 being <5%, and the risk of malignant transformation of TI-RADS 4 being between 5-~20%) needs to be further improved. The present study revealed that the tongue texture index has a linear correlation with TI-RADS. In the future, the tongue texture index with TI-RADS classification could be combined to improve its accuracy and reduce unnecessary biopsy and treatment cost for patients.

The present single-center study has several limitations that are worth mentioning. Firstly, the study population's tongue image results, may be affected by the regional environment (For example: the southeast of China is wet and hot, while the

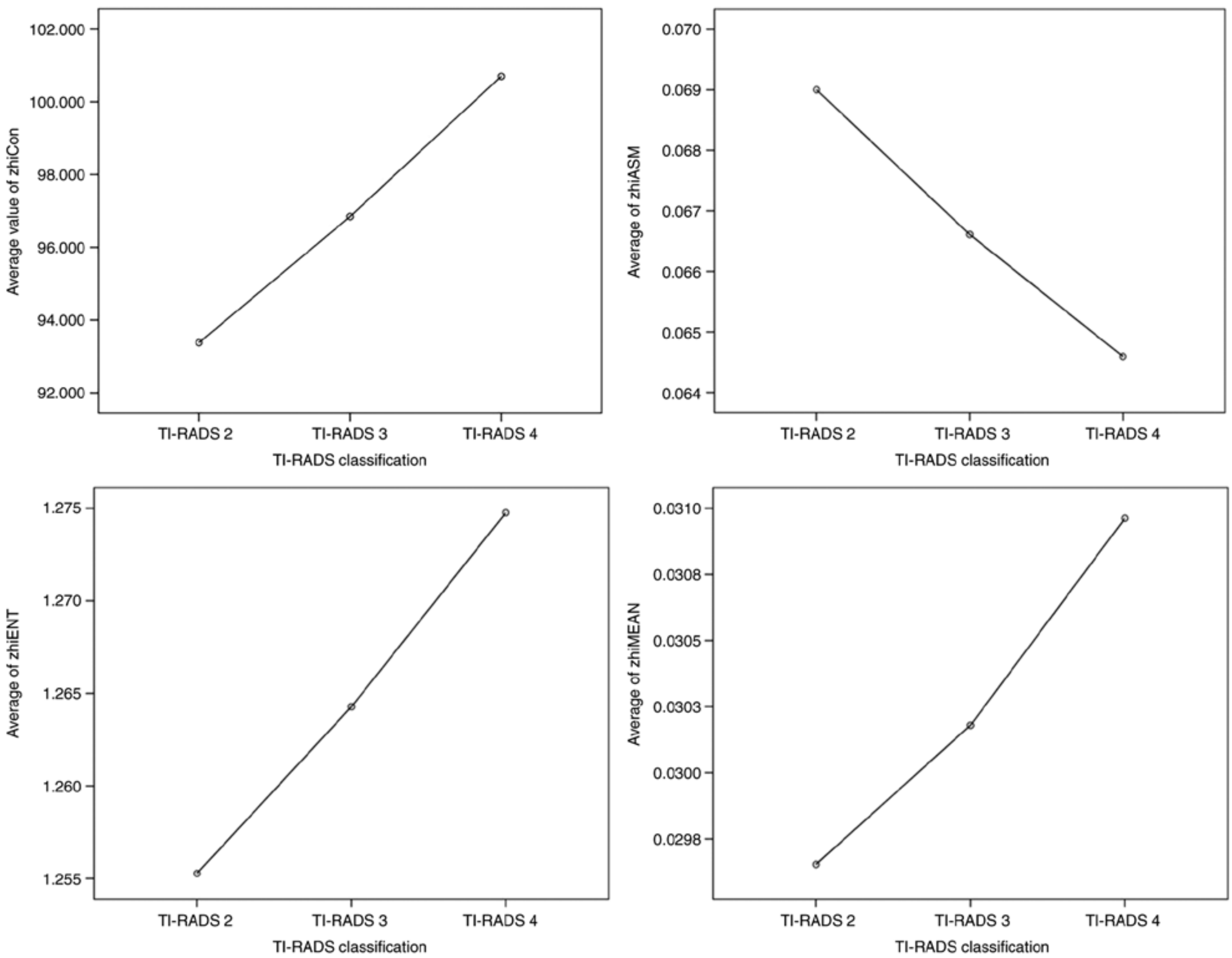

Figure 3. Linear trend analysis plots of tongue image index zhiCon, zhiENT, zhiASM, zhiMEAN. The relationship of the tongue image indexes zhiCon, zhiENT, zhiASM and zhiMEAN values with TI-RADS classification was linear, with zhiCon, zhiENT and zhiMEAN values increasing and zhiASM decreasing with the increase of TI-RADS classification.

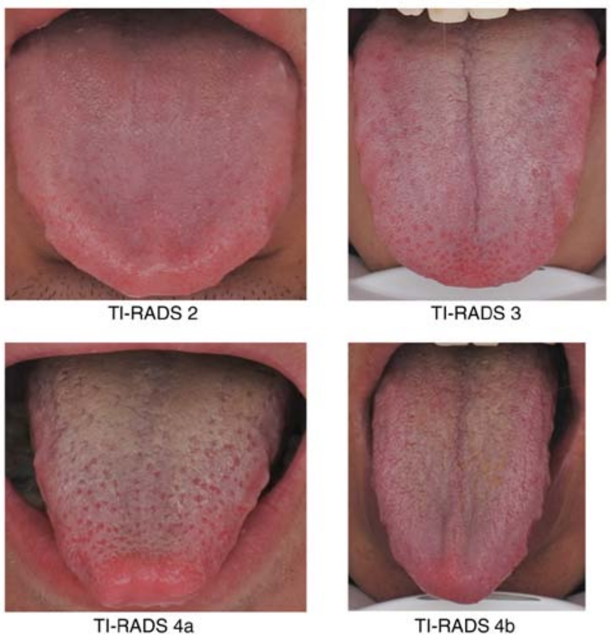

Figure 4. Examples of tongue images of patients in TI-RADS categories. The tongue surface becomes more granular and the tongue texture becomes rougher with the increasing TI-RADS categories. TI-RADS, Thyroid Imaging Reporting and Data System.

northwest and northeast regions are cold and dry, which can cause certain differences in tongue appearance), and some measurement errors may occur. Secondly, in the present study only tongue images were examined by the patients, and the combination of the four diagnoses of diseases in traditional Chinese medicine is the basis. In the future, the objective results should be combined with the information of patients' inquiry, pulse and smell, so as to optimize the diagnosis and treatment measures of patients. Thirdly, the present study tongue image index for judging benign and malignant thyroid nodule reference index, based on ultrasonic TI-RADS classification, malignant change in different classification for different probability as the default condition, further study of tongue images of malignant thyroid nodules should be performed in patients with pathological findings to obtain more accurate results. Fourthly, currently, the present study's research focuses on two aspects: Tongue image capture and image analysis which has consumed a lot of time to be performed. In the near future, image capture and image analysis will be combined by the authors, in an effort, for tongue image diagnosis, to reach the same levels of effectiveness, in terms of speed, as ultrasound diagnosis.

In conclusion, there is a certain relationship between TI-RADS classification of thyroid nodules and tongue texture changes in tongue images. Tongue-based approach may be a significant factor for differentiating the benign and malignant of thyroid nodules.

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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

J-LL, W-HL and Z-HZ contributed to the conception and design of the present study. J-LL, KZ and Z-HZ completed the collation of data. J-LL and Z-HZ confirm the authenticity of all the raw data. SR and J-LL and X-BZ analyzed the data. J-LL wrote the first draft of the manuscript. W-HL and X-BZ critically edited the manuscript. J-LL and W-HL were responsible for the overall project. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved (approval no. 2018KL-050) by The Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (Chengdu, China). Written informed consent was provided by all the patients/participants to participate in the present study.

Patient consent for publication

Patient consent for publication of patient data and associated images was obtained.

Competing interests

The authors declare that they have no competing interests.

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