

Clinical data mining on network of symptom and index and correlation of tongue-pulse data in fatigue population

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Abstract

Background

Fatigue is a kind of non-specific symptom, which is widely found in sub-health and various diseases. It is closely related to people's physical and mental health. Due to lack of objective evidence, it is often neglected in clinical diagnosis, especially in the early stage of disease. A large number of clinical practices and studies have shown that tongue and pulse image are reflection of overall state of the body. Establishing an objective evaluation method for diagnosis of disease fatigue and non-disease fatigue by combining clinical symptom and index and tongue and pulse data is of great significance for timely and effective clinical treatment.

Methods

In this study, 2362 physical examination subjects were divided into healthy control, the group of sub-health fatigue and disease fatigue, used complex network technology to screen out the core symptoms and western medicine indexes of fatigue, respectively. Constructed the core symptom network and the core symptom-index network. At the same time, used canonical correlation analysis to get the associated relationship of tongue and pulse, and analyzed the characteristic of the tongue and pulse data.

Results

There were some similarities between the core symptoms of sub-health fatigue and disease fatigue, as well as differences. Symptom-index associated analysis of disease fatigue showed that the core indexes in the group of disease fatigue group had a significant canonical correlation, with the canonical correlation coefficient was 0.42 ($P < 0.05$). There was no statistically significant correlation between the tongue and pulse data in sub-health fatigue group.

Conclusions

The complex network technology was suitable for the correlation analysis of symptoms and indexes in the fatigue population, and the tongue and pulse objective data had certain diagnostic contribution to the classification of fatigue population.

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Trial registration number: ChiCTR-IOR-15006502; ChiCTR1900026008

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URL of trial registry record: <http://www.chictr.org.cn/showprojen.aspx?proj=11119>;

<http://www.chictr.org.cn/edit.aspx?pid=38828&htm=4> (This is a retrospective registration)

Background

Fatigue is a condition in which the body is unable to begin or maintain a particular intensity of activity, or a pathological manifestation of dysfunction during the initiation or maintenance of voluntary activity. It is not only a physiological manifestation of the body's self-regulation, but also a pathological result of a symptom in some disease states[1]. Study found that more than 50 percent of people were suffered from chronic fatigue and more than 30 percent suffered from fatigue which has a serious impact on their living standards and work efficiency[2]. Some studies have defined fatigue as a symptom of disabling participants with limited physical and mental perception, which is a unique, complex, multifactorial and heterogeneous physiological and pathological state[3]. Fatigue is a kind of non-specific symptom and have certain heritability[4], which has become one of the main factors that harmful to human's physical and mental health. It is ubiquitous in sub-health and various diseases, such as parkinson[5], major depressive disorder[6], schizophrenia[7], cancer[8], which affects human's health, work efficiency and quality of life seriously. Studies have shown that chronic fatigue was most common among women and caucasians and significantly related to depression, mixed anxiety and depressive disorder, and generalized anxiety disorder[9]. The etiology and pathogenesis of fatigue are largely unknown. In recent years, researchers have been exploring various therapeutic measures such as acupuncture and moxibustion[10], spa therapy[11] and chinese herbal medicine[12]. There is still a lacking of objective and effective comprehensive evaluation methods for the diagnosis of fatigue, which leads to the inability to carry out targeted interventions when fatigue occurs in the early stage of disease. Hence it is imperative to establish a comprehensive objective evaluation method for fatigue.

In the diagnosis method of traditional Chinese medicine, tongue and pulse are important objective diagnosis basis. They are comprehensive diagnostic methods based on the body's overall state, which are suitable for the comprehensive evaluation of the body's functional state and have become an important objective basis for health status evaluation and syndrome diagnosis. In recent years, data-driven research and application of tongue and pulse diagnosis have been carried out, and breakthroughs have been made in fatigue quantification and standardization. Artificial Neural Network[13], Support Vector Machine [14], KNN[15] and other machine learning methods has realized the digitalization of TCM tongue and pulse diagnosis, and established the corresponding disease diagnosis model[16; 17]. Fatigue is closely related to human's physical and mental health, research of modern tongue and pulse diagnosis technology applied to fatigue is increasing day by day. Chu et al[18] showed that sphygmogram parameters could be used to objectively evaluate the health status, and sphygmogram parameters such as A_s , h_5 / h_1 and W_2 / t had significant differences among the healthy group, the sub-health group and the disease group. Compared with the healthy group, the value of W_1 / t and W_2 / t of the sub-health patients increased, while h_1 , h_5 , h_5 / h_1 , A_s and A_d decreased. Xu JT et al.[19] established a chronic motion fatigue model to detect the sphygmogram before and after fatigue, and the results showed that after chronic motion fatigue, the sphygmogram changes were mainly characterized by W / t increase, wide main wave, h_4 elevation and forward movement. In addition, it has been confirmed that fatigue and tongue images have certain specificities in tongue color, tongue coating color and tongue shape[20]. Li et

al. [21]found that the a values of tongue body in the fatigue group were higher than those of the control group, the b values of tongue coating were higher than those of the control group, indicating that the tongue color parameters of the fatigue population can provide quantitative objective basis for the diagnosis of TCM in the fatigue population.

Despite the success of current researches on fatigue, there are still a lot of deficiencies need to be overcome. For example, the studies on fatigue symptoms are relatively simple, it is essential to study the correlation between fatigue-related symptoms and to combine analysis of fatigue-related symptoms with disease indexes. In addition, the analysis of objective tongue and pulse data of fatigue based on modern tongue and pulse diagnosis technology is mostly independent, lacking joint analysis of tongue and pulse data. While complex network is the basic framework and highly topological abstraction of complex system. Further analysis of the network through classification, screening and other analytical methods can mine the potential rules of a large number of clinical data. Complex networks are widely used in the analysis of basic laws of Traditional Chinese Medicine [22], network pharmacology[23–25] and combined analysis of TCM syndromes and network pharmacology[26; 27].

Based on the above problems, in this study, 2362 physical examination subjects were divided into healthy control, the group of sub-health fatigue and disease fatigue, used complex network technology and improved node contraction method to screen out the core symptoms and western medicine indexes, respectively. Through constructing the core symptom network and the core symptom- index network, and analyzing the network structure, to establish the distribution rule of fatigue symptom and index. At the same time, use canonical correlation analysis method to get the associated relationship between tongue and pulse data of the fatigue population. Based on symptoms, tongue and pulse data and western medicine indexes, this study tried to explore the characteristics of the fatigue population from different dimensions.

Methods

Study design

From Jul. 2015 to Dec.2018, the physical examination information of 7,025 individuals in the Medical Examination Center of Shuguang Hospital affiliated to Shanghai University of Traditional Chinese Medicine was collected. A total of 361 in the sub-health population and 1529 in the disease population with fatigue symptoms were further selected.

Each disease population was determined by four clinicians according to western medicine physical examination indexes, using the health status assessment questionnaire scale and the Information Record Form of Four Diagnosis of Traditional Chinese Medicine (Copyright No. : 2016Z11L025702) designed by the sub-health research group of the "863 Plan" to judge health and sub-health, After excluding of all disease population, if the H20 score was between 60-79, it was considered as a sub-health population, and if the H20 score was between 80-100, it was considered as a healthy population.

The overall flow diagram of this study was shown in Fig. 1.

Collect the Information of the Four Diagnostic Methods of TCM and Physical and Chemical Indexes

The four-diagnostic scale of Traditional Chinese Medicine includes 25 categories and 256 sub-items. According to the degree of symptoms, the scale was divided into three levels: no, mild and severe, which are marked by 0, 1 and 2 respectively.

We used TFDA-1 tongue diagnostic instrument (software copyright registration No.:2018SR033451) and PDA-1 pulse diagnostic instrument (Patent No.:ZL201620157027.6) which independently developed by the National Key Research and Development Program "Traditional Chinese Medicine Intelligent Tongue Diagnosis System Research and Development" to collect the clinical tongue and pulse data. In addition, clinical indexes mainly include a total of 191 indexes such as blood routine, urine routine, liver and kidney function, tumor markers, electrocardiogram and imaging examination. The questionnaire and collection of tongue and pulse were completed by researchers from Shanghai University of Traditional Chinese Medicine with unified and standardized training to ensure consistency and accuracy in the interpretation of sample collection results. The tongue image acquisition equipment and the analysis interface were shown in Fig.2 and Fig.3, Fig.2 (A) and Fig.2 (B) were the front view and profile view of the tongue diagnosis instrument respectively, the main measurement parameters of the sphygmogram were shown in Fig. 4, Fig.4(A) was the PDA-1 pulse diagnosis instrument and supporting equipments, Fig.4(B) was the sphygmogram of PDA-1 diagnosis pulse instrument.

The color parameters of tongue image in Fig. 3 come from four color spaces:[28-30] RGB, HSI, Lab and YCrCb, They are R (red), G (green) and B (blue), H (hue), S (saturation), I (brightness), L (lightness), a (red-green axis), b (yellow-blue axis), Y (brightness), Cr (the difference between the red part of the RGB input signal and the brightness value of the RGB signal), Cb (the difference between the blue part of RGB input signal and the brightness value of RGB signal), perAll and perPart.

The parameters of sphygmogram in figure 4(B), h represents amplitude height. h_1 is the main amplitude, h_3 is the heavy wave front wave amplitude, h_4 is the dicrotic notch amplitude, h_5 is the gravity wave amplitude, t_1 is the time value from the start point to the crest point of the main wave, t_4 The time value from the start point to the dicrotic notch, t_5 is the time value from the dicrotic notch to the end point, t is one pulsating period, and W is divided into W_1 and W_2 , W_1 is 1/3 height of main wave, W_2 is 1/5 height of main wave.

Normalized Data Entry and Extraction

Excel and Python3.7 were used to match, combine and collate the data to establish the symptom data sets and western medicine index data sets respectively. A total of 494 symptoms and biochemical test indexes data were collected, including 254 symptoms of Traditional Chinese medicine and 240 western medicine indexes. The data were binarized. The positive symptoms of TCM were marked as "1" and the negative symptoms as "0". Negative qualitative data of biochemical index of Western medicine were

recorded as "0", positive data including weak positive (+) and strong positive (++ or +++) were recorded as "1", quantitative data within the normal range were recorded as "0", and higher or lower than the normal range was recorded as "1".

Screening of Symptoms and Indexes

According to the characteristics of the data, the improved node contraction method was used to quantitatively analyze the nodes in the network. The basic idea of node contraction method is to first shrink the nodes in the network one by one, and then compare the changes of network aggregation degree, so as to achieve the purpose of ranking the importance of nodes. The improved node contraction method [31] comprehensively considers the weight of edges in the weighted network. In this study, the weight of edges represents the number of simultaneous occurrences of two connected nodes. The larger the weight is, the closer the relationship between the two indexes. So here we choose the sum of the edge weights as the point weights. In the weighted network, the corresponding concept of node degree is node strength. After the specific definition of node strength, the definition of network cohesion is extended to the weighted network. Network cohesion refers to the reciprocal of the product of the number of nodes n and the average shortest distance L . In order to quantitatively describe the degree of network cohesion, network cohesion [32] is defined as follows (f1) :

$$\partial(WG) = \frac{1}{s \times l} = \frac{1}{\sum_1^n N_i \sum_{j \in N_i} w_{ij} \times \frac{\sum_{i \neq j \in V} d_{ij}}{n \times (n-1)}} \quad (1)$$

In the above formula, S is actually the sum of the average node strength of the network, the value of which is the strength of each node divided by the number of neighboring nodes of the node. L is the average shortest distance of the unweighted network corresponding to the weighted network after thresholding. The definition of node importance is expressed in $IMC(V_i)$ see formula (2), $\partial(G * V_i)$ refers to the condensation degree of a network after node contract and fusie.

$$IMC(V_i) = 1 - \frac{\partial(WG)}{\partial(WG * V_i)} \quad (2)$$

In this study, the improved node contraction method takes the degree, betweenness and edge weight of nodes into consideration, which is basically consistent with the purpose and requirement of importance of each node.

Construction and Analysis of Complex Network

MATLAB software (MATLAB R2016a) was used to process binary data, and the core symptoms and indexes data were selected according to the importance of nodes. The top 10 data were selected for network construction and analysis. In this paper, Pajek software (Pajek 64 5.08) was used for network construction and analysis. The size of nodes and the thickness of edges were drawn according to the sum of the weights of nodes' edges (namely the strength). Edited and defined the color and label of each

node, selected the appropriate output mode, and manually adjusted the node position to output the network diagram to complete the construction of each network.

Statistical Analysis

SPSS (Version 23.0) software was used for statistical analysis of the data. The measurement data were expressed as "X ± S", ANOVA was performed for homogeneity of variance and homogeneity of variance among groups, Kruskal-wallis H test was performed for nonnormal distribution data, use GraphPad Prism Version 8.0 for Canonical Correlation Analysis, all the test results were double-tailed test, test level was $\alpha=0.05$, and the difference was statistically significant when $P < 0.05$.

Results

Data Set for Fatigue Group

There were 361 people in the group of sub-health fatigue, 1529 people in the group of disease fatigue and 742 people in the healthy control. The patients in the group of disease fatigue were mainly hypertension, diabetes, hyperlipidemia and fatty liver, and the basic statistical characteristics of the health, sub-health and disease groups were shown in Table 1.

Table 1

Statistical table of basic information of the participants in the health control, sub-health fatigue and disease fatigue.

Group	N	male	female	Age	BMI	
		N(%)	N(%)	(x ± s, year)	(Kg/m ²)	
Health	742	553(74.5)	189(25.5)	32.52 ± 10.16	22.71 ± 3.08	
Sub-health	361	215(59.6)	146(40.4)	34.64 ± 9.45**	22.74 ± 3.46	
Disease	Hypertension	311	228(73)	83(27)	48.56 ± 13.94**##	25.51 ± 3.41**##
	Diabetes	157	127(81)	30(19)	54.04 ± 12.79**##	25.95 ± 3.67**##
	Hyperlipemia	518	373(72)	145(28)	45.87 ± 12.69**##	24.97 ± 3.27**##
	Fatty liver	442	334(76)	108(24)	45.10 ± 13.20**##	26.57 ± 3.06**##
*vs. healthy control $P < 0.05$, ** vs. healthy control, $P < 0.01$.						
#vs. the group of sub-health $P < 0.05$, ## vs. the group of sub-health $P < 0.01$.						

Construct and Analyze of Symptom Network of the Group of Sub-health Fatigue

MATLAB was used for data processing of the group of sub-health fatigue with complete symptoms. The binary TCM symptom data was converted into ".NET" format, use Pajek software to draw the network, and the symptom network was shown in Fig. 5.

As the total network has many nodes and complex network relationships, the relationship between its core nodes could not be well described. Therefore, selected the core nodes according to the importance of nodes $IMC(V_i)$ was necessary, and then used Pajek software to draw the core symptom network. The network was shown in Fig. 6, in the network the size of nodes in network represented the strength of nodes, the thickness of edges represented the weight between nodes, and the core symptoms were shown in Table 2.

Table 2
Core symptom of the group of sub-health fatigue

Index	Symptom	$IMC(V_i)$
TC1	white tongue coating	0.999
LP1	headache	0.997
TC2	yellow tongue coating	0.996
QP1	sour	0.996
EM7	dreaminess	0.994
EM3	irritability	0.994
THA4	chest distress	0.992
HE13	xerophthalmia	0.991
TC6	thick coating	0.991
EM6	insomnia	0.989

Analyze the network, take the symptom- index associated pairs whose normalized weight was greater than 0.5, and the associated results were shown in Table 3.

Table 3

Associate analysis of core symptom- symptom of group of sub-health fatigue

Symptom		Weight
LP1	QP1	1.000
TC1	QP1	0.905
	HE13	0.833
	LP1	0.810
	TC6	0.750
	EM3	0.679
	EM6	0.643
	EM7	0.631
TC2	TC6	0.512
QP1	HE13	0.464
Construct and Analyze of Symptom and Index Network of the Group of Disease Fatigue		

Used the same method to draw a large network of symptom and index of the group of disease fatigue, as shown in Fig. 7.

In the same way as the sub-health fatigue group, selected the core symptoms and indexes and draw networks of disease fatigue. The symptom and index networks were shown in Fig. 8 and Fig. 9, the size of nodes in the figure represented the strength of nodes, while the thickness of edges represented the weight between nodes, and the core symptoms and indexes and node importance rank were shown in Table 4 and Table 5.

Table 4
Core symptom and node importance rank of the group of disease fatigue

Index	Symptom	IMC(Vi)
TC1	white tongue coating	1.000
HE1	dizziness	1.000
TC2	yellow tongue coating	1.000
QoP1	sour	1.000
EM7	dreaminess	1.000
TC6	thick coating	1.000
PU15	string-like pulse	1.000
TC11	greasy coating	1.000
EM6	insomnia	1.000
EM3	irritability	0.999

Table 5
Core index and node importance rank of the group of disease fatigue

Index	Index	IMC(Vi)
BRT13	basophil	1.000
BRT20	platelet distribution width	1.000
SBP	systolic blood pressure	1.000
BRT12	percentage of monocyte	1.000
DBP	diastolic blood pressure	1.000
RUT5	PH of urine	1.000
BRT8	hemoglobin	1.000
BRT10	hematocrit	1.000
BI15	uric acid	1.000
BMI	body mass index	1.000

The relationships between symptoms and western medicine indexes are very complicated in the actual clinical diagnosis of disease and syndrome. The combined diagnosis of disease and syndrome cannot rely on symptoms or biochemical indexes solely. It is necessary to combine symptoms and indexes to

analysis together. Its core symptom-indicator interaction edges were shown as cyan lines. The core symptom-indicator network was shown in Fig. 10.

Analyzed the network, took the top 10 pairs of core symptom-symptom pairs and index-index pairs respectively, and the associated analysis results were shown in Table 6 and Table 7.

Table 6
Associated analysis of core symptom- symptom of the group of disease fatigue

Symptom		Weight
TC1	QP1	0.187
TC2	TC6	0.167
TC1	EM3	0.153
TC2	TC11	0.149
TC1	HE1	0.142
TC1	EM7	0.137
PU15	TC1	0.134
TC1	EM6	0.132
TC6	TC11	0.129
TC2	QP1	0.123

Table 7
Associated analysis of core index-index of the group of disease fatigue

Index		Weight
BRT13	SBP	1.000
BRT13	BRT20	0.921
BRT13	BRT12	0.913
BRT20	SBP	0.908
SBP	BRT12	0.902
DBP	SBP	0.873
BRT13	DBP	0.868
BRT20	BRT12	0.824
DBP	BRT12	0.782
BRT20	DBP	0.782

The core symptom- index associated results were further selected, and the top 10 symptom-indicator pairs were shown in Table 8.

Table 8
Associated analysis of core symptom- index of the group of disease fatigue

Symptom	Index	Weight
TC1	SBP	0.546
	BRT13	0.545
	BRT20	0.494
	BRT12	0.491
	DBP	0.474
TC2	BRT13	0.376
	SBP	0.372
	BRT12	0.342
	BRT20	0.338
	DBP	0.326

In conclusion, the research results show that white coating, yellow coating, sour, dreaminess, irritability, thick coating and insomnia are the common symptoms of the two fatigue groups. The main difference was that the node importance of the same symptom varies in different population networks, indicating that the diagnostic contribution rate of the same symptom to the two groups was different. Headache, chest distress and xerophthalmia were more significant in the group of sub-health fatigue, while dizziness, string-like pulse and greasy coating were more significant in the group of disease fatigue. The most common abnormal indexes in the fatigue group were basophil, platelet distribution width, systolic blood pressure, percentage of monocyte, diastolic blood pressure, PH of urine, hemoglobin, hematocrit, uric acid, and body mass indicator. Symptom- index associated analysis showed that systolic blood pressure, basophil, platelet distribution width, percentage of monocyte, and diastolic blood pressure were closely related to white coating and it was also related to yellow coating to some extent.

Canonical Correlation Analysis Of Tongue And Pulse Parameters

Individuals with outliers and extreme values in tongue and pulse data of three groups were excluded, rearrange the sample of the three groups. Finally, 551 were included in the health control, 252 in the group of sub-health fatigue and 1,160 in the group of disease fatigue.

Canonical Correlation Analysis verifies the overall correlation between one set of variables and another. The results showed that there was a certain correlation between the tongue and pulse data of healthy control and the group of disease fatigue. The correlation coefficient of tongue and pulse data in the healthy control was 0.475 ($P < 0.05$), and tongue characteristic parameters were mainly affected by TB-Cb, TB-b, TB-H and TC-Cb (canonical correlation coefficients were -0.435 , 0.431 , 0.429 and -0.374 , respectively, $P < 0.05$). Pulse characteristic parameters were mainly affected by h_1 and h_1/t_1 (canonical correlation coefficients were 0.388 and 0.378 , respectively, $P < 0.05$, as shown in Fig. 11(A)). The correlation coefficient of tongue and pulse data in the group of disease fatigue was 0.420 ($P < 0.05$), and tongue characteristic parameters were mainly affected by perAll, TC-Cr, TB-Cr, TB-Cb, TB-b (canonical correlation coefficients were -0.723 , 0.697 , 0.649 , -0.603 and 0.590 , respectively, $P < 0.05$). Pulse characteristic parameters were mainly affected by h_4 , h_4/h_1 , h_3/h_1 , h_3 and W_2/t (canonical correlation coefficients were -0.621 , -0.609 , -0.507 , -0.480 and -0.446 , respectively, $P < 0.05$, as shown in Fig. 11(B)). There was no statistically significant correlation between the tongue and pulse data in the group of sub-health fatigue.

Discussion

Fatigue is an important early warning signal of abnormal health status. It should be treated in time to prevent its further development into a more serious disease. At present, there are two main reasons for the difficulties in fatigue research. First, the mechanism of fatigue is complex, and there is still a lack of diagnostic criteria for fatigue, the second is lack of effective fatigue evaluation model [33]. A study of the

relationship between CFS and depression based on artificial intelligence has found that the two diseases share some of the same biomarkers[34]. Although diagnostic criteria for CFS have been proposed, there is still a lack of convincing models to explain the etiology and pathogenesis of it as an independent and unique disease. Different studies have different explanations for the pathogenesis of fatigue symptoms. At present, the mechanism of fatigue is mainly related to dopamine[35], HPA axis dysfunction[36], compensation for negative feedback inhibition[37], and serotonin function disorder[38]. The above four theories are widely recognized.

Studying the interrelationship between fatigue-related symptoms is helpful to further determine the diagnosis direction of fatigue-related diseases. In this study, complex network technology was used to screen out the main symptoms and indexes of fatigue patients in physical examination population, as well as the interaction between symptoms and indexes. Headache, chest distress and xerophthalmia were more significant in the group of sub-health fatigue, headache and chest distress were generally manifested as qi stagnation syndrome, and xerophthalmia was the common clinical manifestation of jinye deficient syndrome. String-like pulse, greasy coating and dizziness were more significant in the group of disease fatigue. The clinical significance of string-like pulse is mainly about liver and gallbladder disease, pain, phlegm and retained fluid, consumptive disease, and also the stomach gas decline. The clinical significance of greasy coating is phlegm-damp, phlegm and retained fluid, dyspepsia. These two symptoms are consistent with common pathological manifestations of the disease. And dizziness is the concomitant symptom of disease such as hypertension, hypoglycemia, anaemia and oncosis. Basophil, platelet distribution width, percentage of monocyte, hemoglobin, hematocrit were blood routine items. The value of PH of urine and uric acid are routine items of urine examination, abnormal of these two indexes mostly indicates abnormal renal function. BMI mostly reflects human metabolism, and studies have shown that lipid metabolism disorder plays an important role in the formation of tongue coating[39]. It can be seen that abnormal blood routine, renal function, blood pressure and basic metabolism are more common in patients with fatigue. Associated analysis of symptom and indexes can better explore the nature of disease. It reported for the first time that ALT was increased in 177 patients with viral hepatitis, and the thick coating is predominant. The serum glutamyl transferase level is related to the thickness of tongue coating in patients with acute jaundice viral hepatitis. It provides a new perspective for the diagnosis of diseases[40]. In this study, symptom-index associated analysis showed that systolic blood pressure, basophil #, platelet distribution width, percentage of monocyte, and diastolic blood pressure were closely related to white coating and it is also related to yellow coating to some extent. The clinical significance of white coating in disease state is mainly surface syndrome, cold syndrome and dampness syndrome. Thus it can be seen that fatigue population is mostly seen in surface syndrome, cold syndrome and dampness syndrome. This analysis is helpful to better understand the core symptoms, the interaction between symptoms and the distribution of syndromes of the fatigue groups, in order to provide theoretical basis for the rapid and accurate diagnosis.

Fatigue as a comprehensive performance of the whole body, it is necessary to analyze the relationship between the indexes. Canonical correlation analysis method was used for combined analysis of tongue and pulse data. The results show that the overall correlation of tongue and pulse data in the healthy

group is higher than that in the disease fatigue group. The reason for the result may be that there are many kinds of diseases in patients with fatigue, while the healthy control is relatively single. In addition, the correlation between tongue and pulse parameters in the disease fatigue was significantly higher than that in the healthy control. In other words, when the human body is in the state of disease fatigue, their tongue and pulse parameters are more closely related. It indicates that when the body presents pathological status, the tongue and pulse data have a consistent overall change trend, and the tongue and pulse data of patients with disease fatigue have obvious aggregation characteristics. In addition, the indexes of tongue coating parameters PerAll, TB-Cr, TB-Cb, TB-b, TC-Cr, TC-Cb, TC-b are representative of comprehensive variables, and the indexes of pulse parameters h_4 , h_4/h_1 , h_3/h_1 and h_3 are representative of comprehensive variables.

This study still has some limitations. In the future study, complexion spectral data can be added on the basis of tongue and pulse data. Molecular biology research can be further added to supplement genomics, proteomics and metabolomics researches. Integrating more objective indexes that can objectively evaluate fatigue will be more productive to analyze this phenomenon and its mechanism. In addition there still lacks treatment guidance and intervention for the fatigue population in this study, which we will be improve in the future.

Conclusion

In summary, this study constructed the fatigue related symptom network and symptom-index network, and analyzed the data characteristics of tongue and pulse in fatigue population, the distribution of symptoms, indexes, data of tongue and pulse in different fatigue population was also revealed. It provided an objective basis for establishing the data evaluation of fatigue state, we are looking forward to establishing a fatigue evaluation method based on objective data of tongue and pulse in the future.

Abbreviations

TCM: Traditional Chinese Medicine; KNN: K Nearest Neighbor; ANOVA: Analysis of Variance; BMI: Body Mass Index; TB: Tongue Body; TC: Tongue Coating; ALT: Alanine Transaminase; CFS: Chronic Fatigue Syndrome

Declarations

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Authors' contributions

XJ and TL developed the study concept and design. SY and HX drafted the initial manuscript. SY, CJ and CL performed the statistical analyses. HJ, MX, JT, YX, LJ, BZ, LJ, WY, FH, WJ, LY, BJ and GX provided critical revisions. All authors read and approved the final manuscript.

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Availability of data and materials

The experimental data will not be shared as it involved in privacy conditions.

Ethics approval and consent to participate

The study protocol was approved by the IRB of Shuguang Hospital affiliated with Shanghai University of TCM (No. 2018-626-55-01). Written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

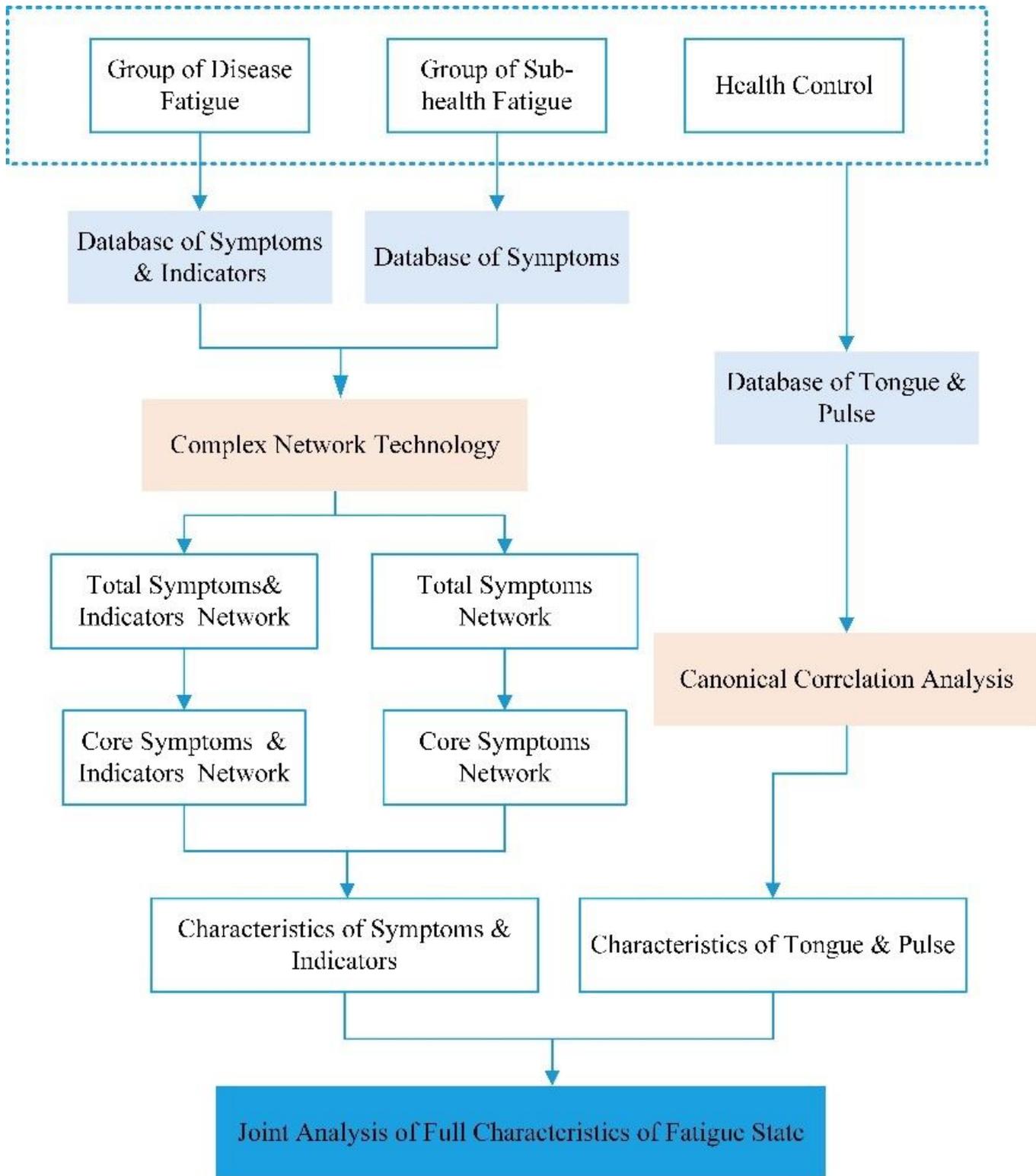


Figure 1

Overall flow diagram.

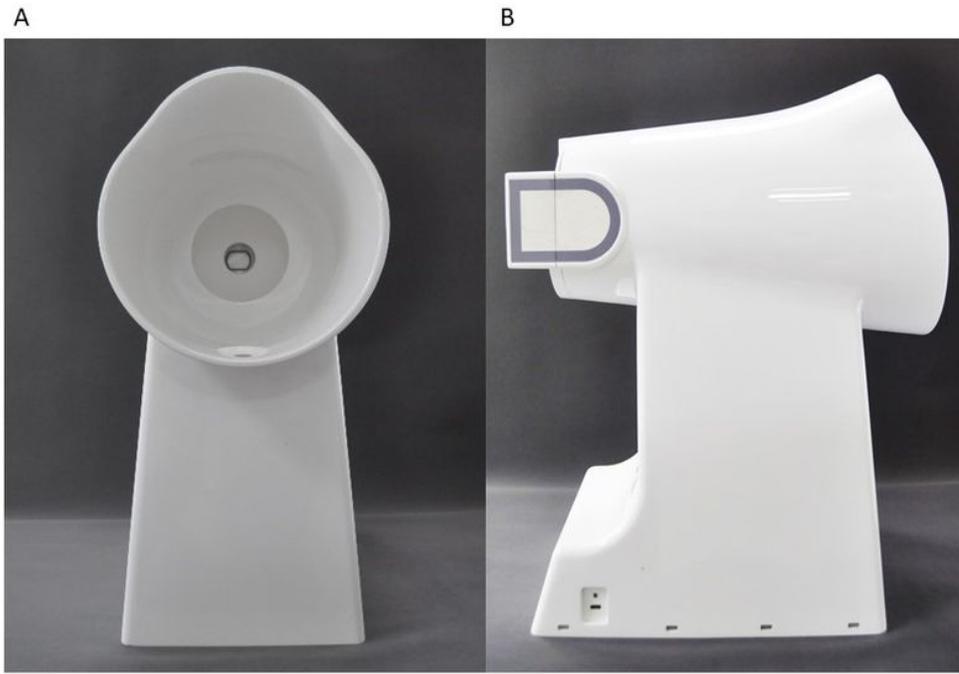


Figure 2

Figures of TFDA-1 tongue diagnosis instrument. (A): Front view.(B): Profile view.

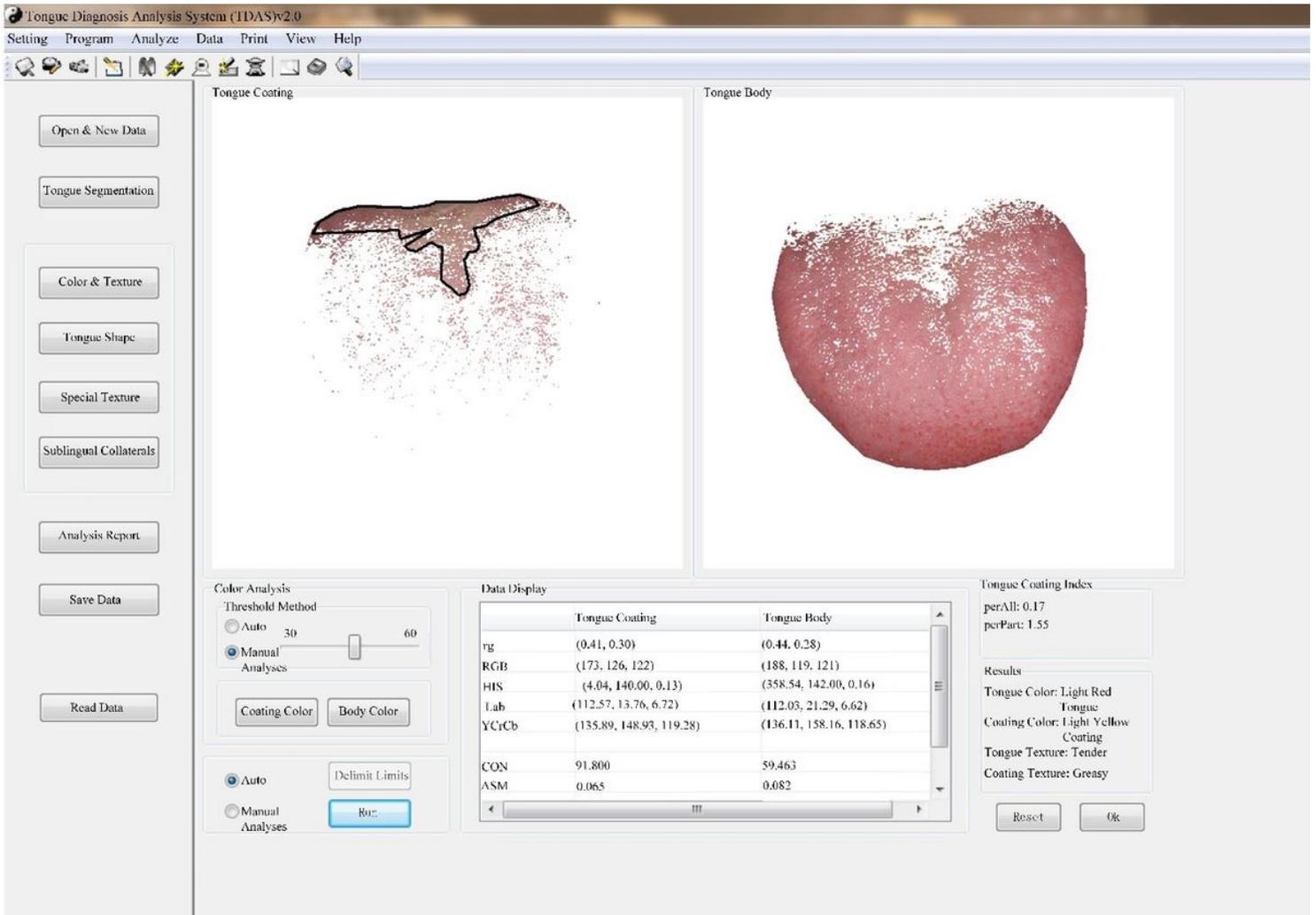


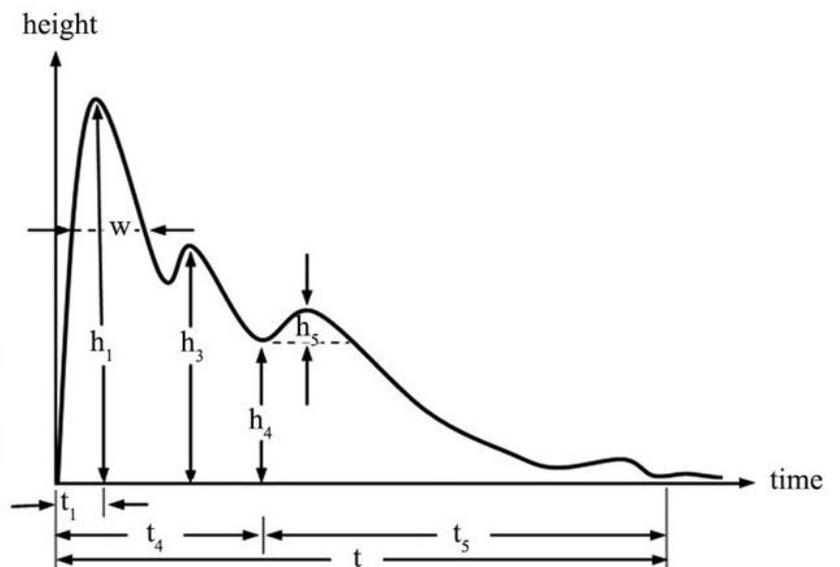
Figure 3

Tongue image analysis interface.

A



B



Network of core symptom of the group of sub-health fatigue. TC1:white tongue coating; LP1:headache; TC2:yellow tongue coating; QP1:sour; EM7:dreaminess; EM3:irritability; THA4:chest distress; HE13:xerophthalmia; TC6:thick coating; EM6:insomnia.

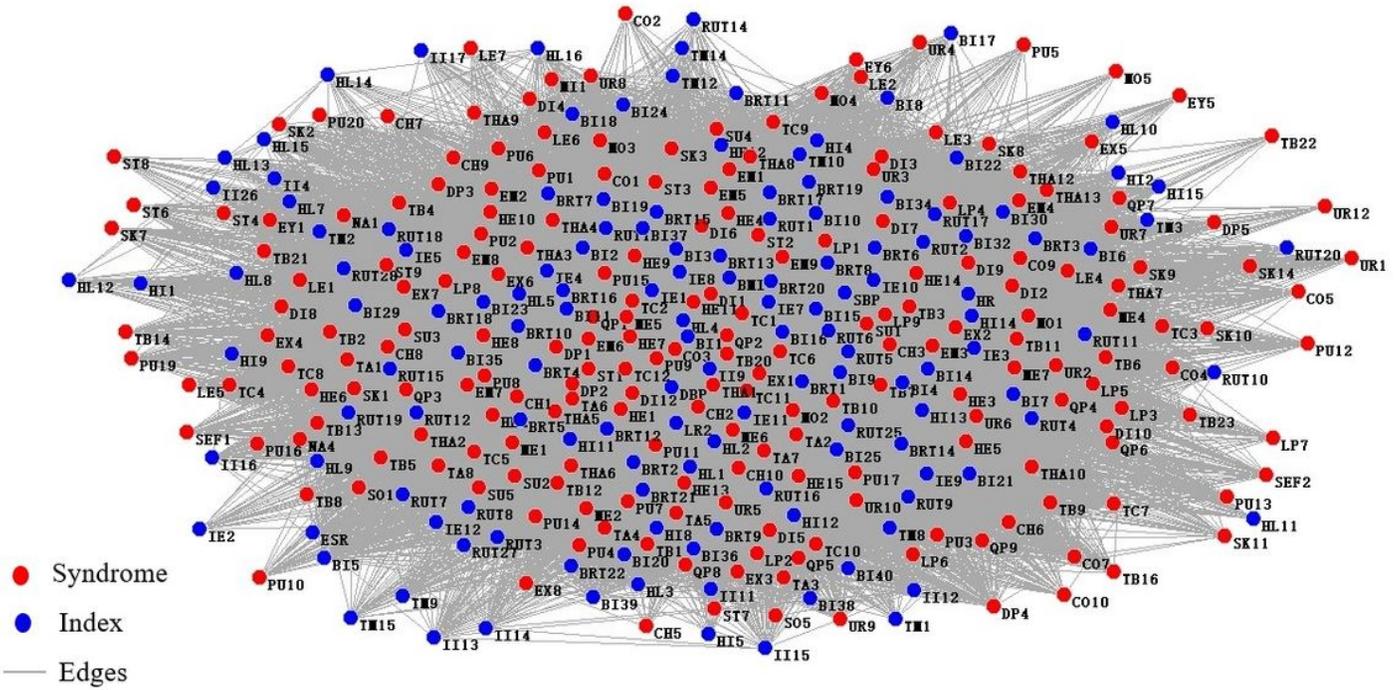


Figure 7

Symptom and index network of the group of disease fatigue.

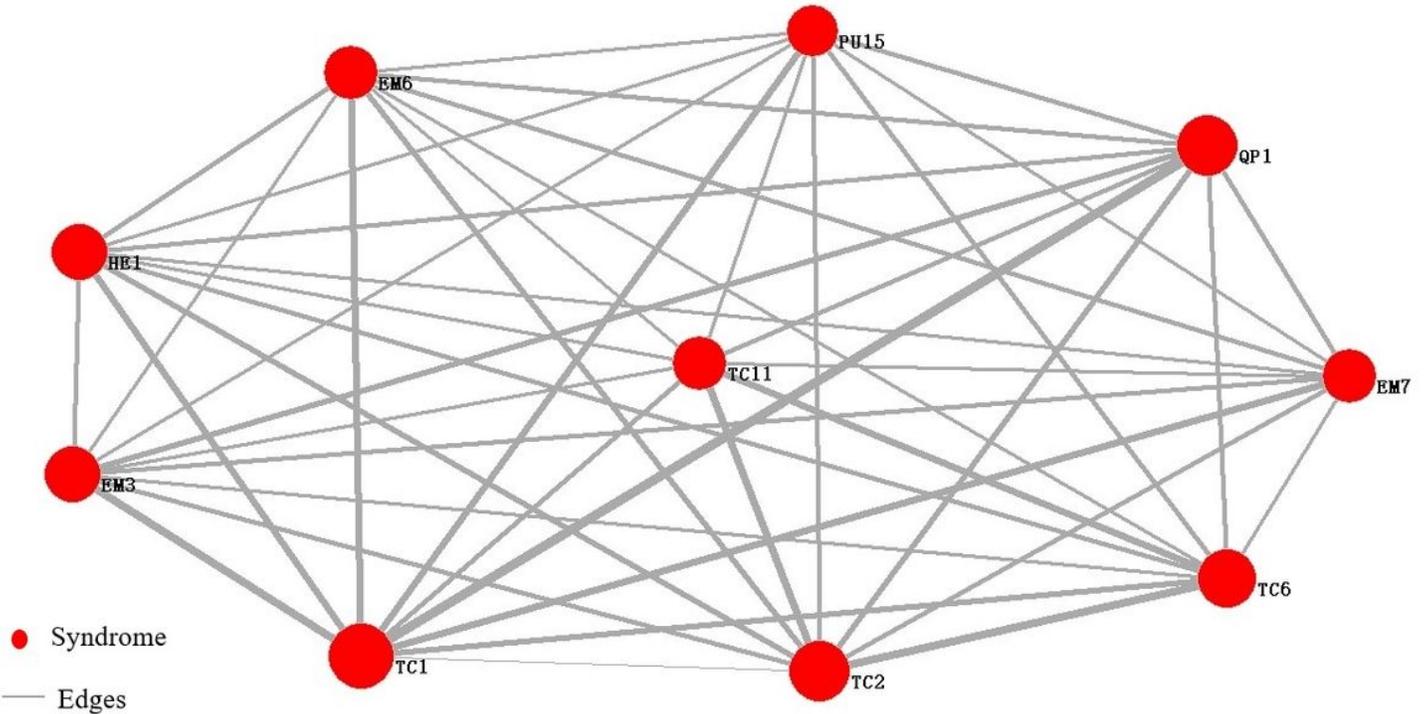


Figure 8

Network of core symptom of the group of disease fatigue. TC1:white tongue coating; HE1:dizziness; TC2:yellow tongue coating; QoP1:sour; EM7:dreaminess; TC6:thick coating; PU15:string-like pulse; TC11:greasy coating; EM6:insomnia; EM3:irritability.

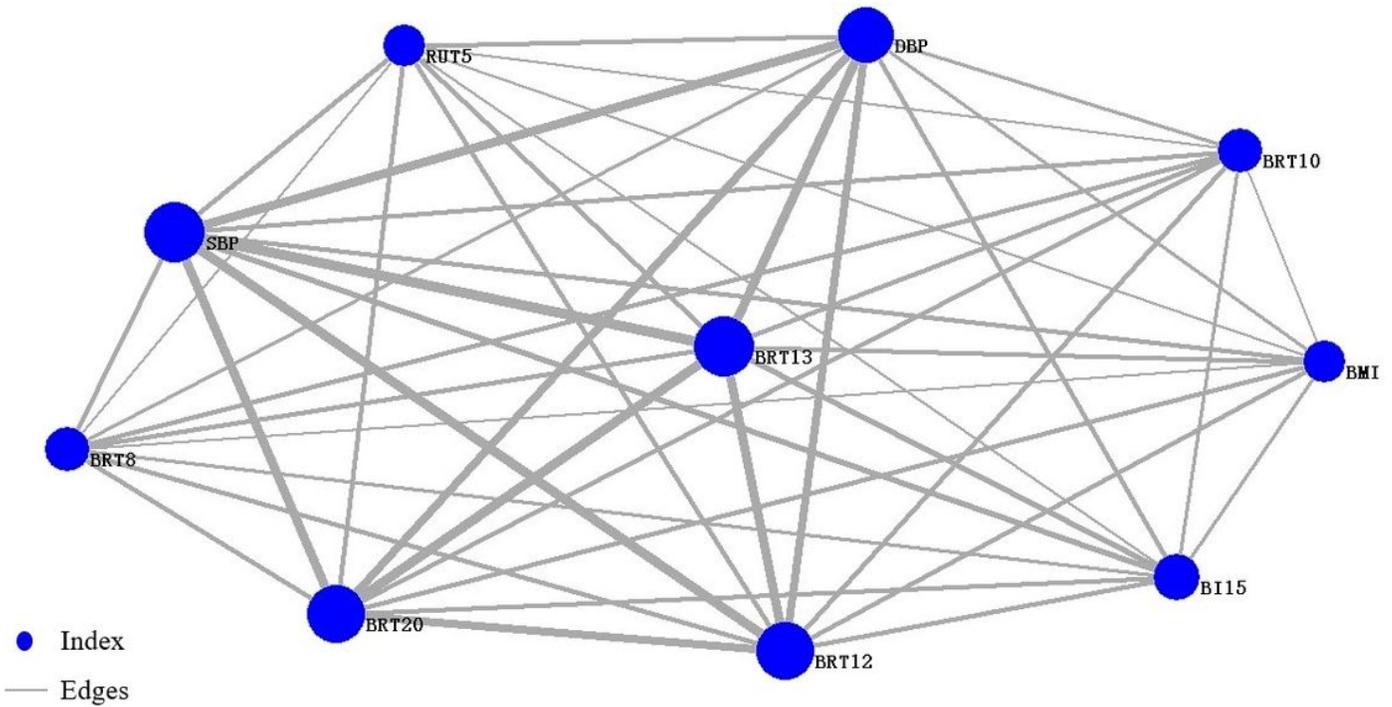


Figure 9

Network of core index of the group of disease fatigue. BRT13:basophil; BRT20:platelet distribution width; SBP:systolic blood pressure; BRT12:percentage of monocyte; DBP :diastolic blood pressure; RUT5:PH of urine; BRT8:hemoglobin; BRT10:hematocrit; BI15:uric acid; BMI :Body mass index.

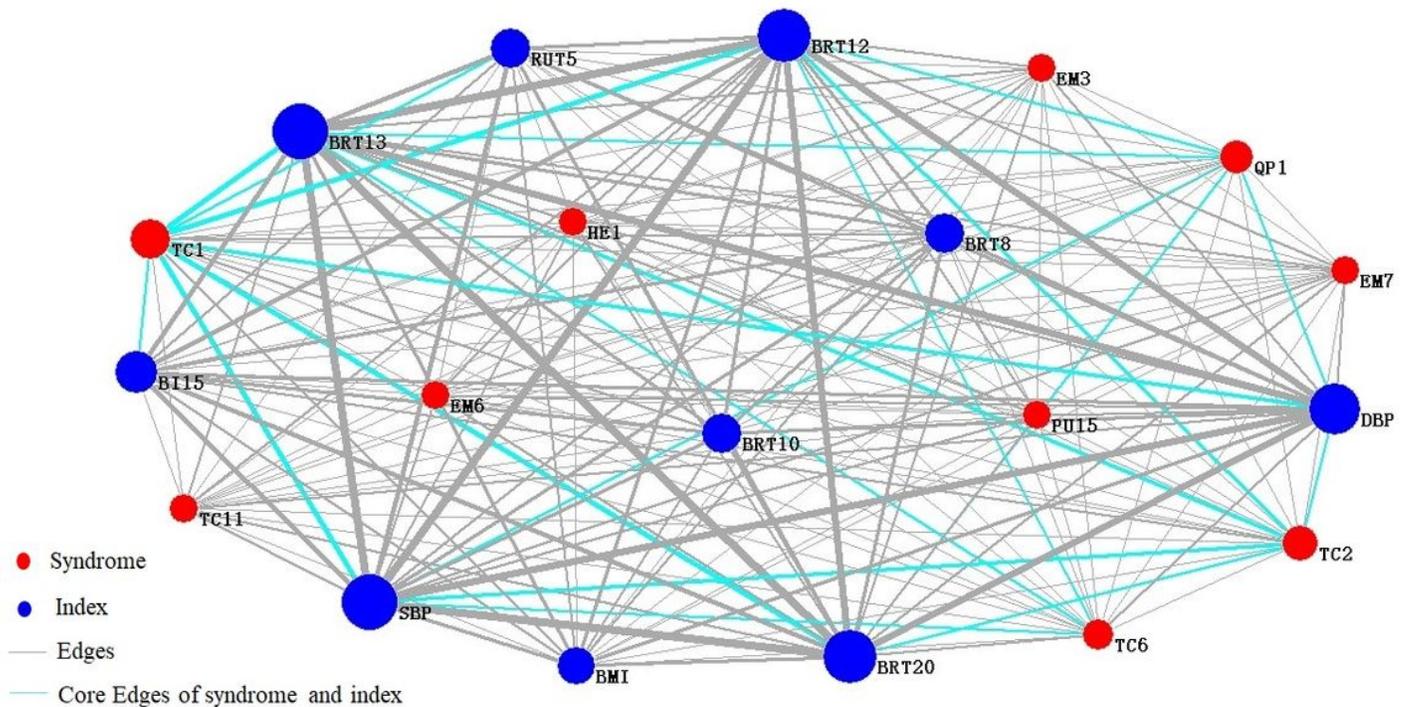


Figure 10

Network of core symptom-indicator of the group of disease fatigue. TC1:white tongue coating; HE1:dizziness; TC2:yellow tongue coating; QoP1:sour; EM7:dreaminess; TC6:thick coating; PU15:string-like pulse; TC11:greasy coating; EM6:insomnia; EM3:irritability; BRT13:basophil; BRT20:platelet distribution width; SBP:systolic blood pressure; BRT12:percentage of monocyte; DBP :diastolic blood pressure; RUT5:PH of urine; BRT8:hemoglobin; BRT10:hematocrit; BI15:uric acid; BMI:body mass index.

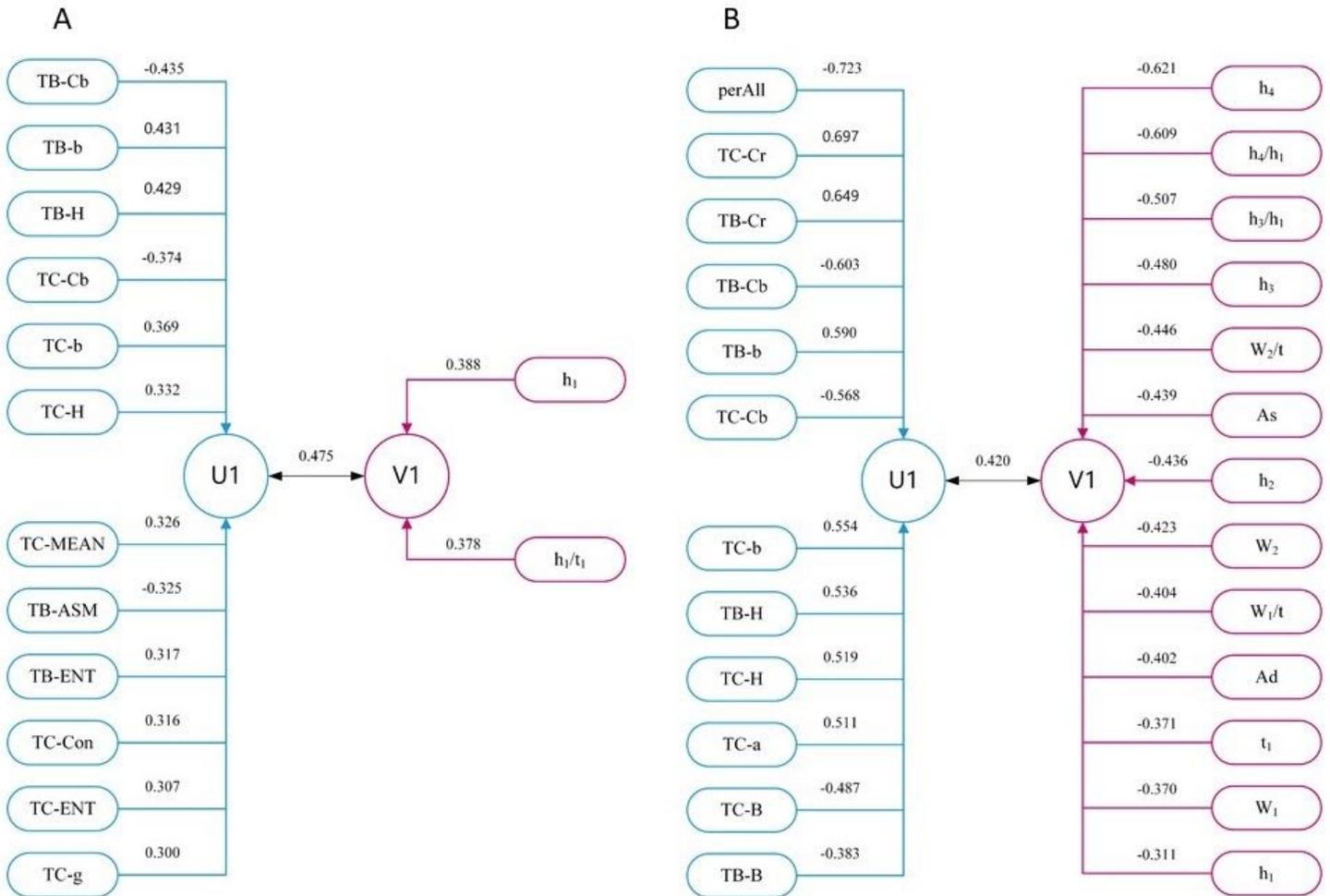


Figure 11

Structure diagram of canonical correlation analysis of tongue and pulse parameters. The left indexes of Figure A and Figure B are the parameters of tongue, and the right indexes are the parameters of pulse. The prefix TB represents the tongue body index, and prefix TC represents the tongue coating index. U1 is the representative comprehensive variable extracted from the tongue parameters, V1 is the representative comprehensive variable extracted from the pulse parameters. (A): Healthy control group. (B): The group of disease fatigue.