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RESEARCH ARTICLE

Symptom network topological features predict the effectiveness of herbal treatment for pediatric cough

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Abstract **Pediatric cough is a heterogeneous condition in terms of symptoms and the underlying disease mechanisms. Symptom phenotypes hold complicated interactions between each other to form an intricate network structure. This study aims to investigate whether the network structure of pediatric cough symptoms is associated with the prognosis and outcome of patients. A total of 384 cases were derived from the electronic medical records of a highly experienced traditional Chinese medicine (TCM) physician. The data were divided into two groups according to the therapeutic effect, namely, an invalid group (group A with 40 cases of poor efficacy) and a valid group (group B with 344 cases of good efficacy). Several well-established analysis methods, namely, statistical test, correlation analysis, and complex network analysis, were used to analyze the data. This study reports that symptom networks of patients with pediatric cough are related to the effectiveness of treatment: a dense network of symptoms is associated with great difficulty in treatment. Interventions with the most different symptoms in the symptom network may have improved therapeutic effects.**

Keywords pediatric cough; complex network; symptoms; traditional Chinese medicine; electronic medical records

Introduction

Cough is a common symptom of pediatric respiratory system disease, which is also considered the disease condition in the category of pediatric pulmonary disease of traditional Chinese medicine (TCM). It is a protective reflex, which is a component of normal respiratory physiology that enhances mucociliary function and clears excessive secretions and airway debris from the respiratory tract and is a very common symptom of respiratory disease [1,2]. Most episodes of cough in children are acute (less than 2 weeks) and secondary to a lower respiratory infection. A cough that persists beyond 2 weeks can be classified as prolonged acute (2–4 weeks) or chronic (more than 4 weeks) [3,4].

At present, most TCM clinical studies on pediatric cough focus on evaluating or confirming the effectiveness of different treatment principles and prescriptions. For example, Feng *et al.* explored the empirical knowledge of a highly experienced physician in treating pediatric cough with classical prescription [5]. Although pediatric cough has been investigated in various fields (e.g., etiology, symptom, and therapy), its incidence remains high. Highly experienced TCM physicians may also encounter some patients who have poor efficacy. Current studies investigate the relationship between the independent effect of symptoms and the diagnosis and treatment of symptoms. The diversity of the co-occurred symptoms of patients may be the cause for different treatment effects. In TCM clinical settings, the accompanying symptoms, such as nasal congestion and expectoration, of pediatric cough patients have significant contributions to syndrome (i.e., Zheng) differentiations, which involve complicated interactions

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among different symptoms [6].

Network medicine, which aims to gain an understanding of human disease from the perspectives of systems biology and complex networks, is a rapidly developing field that has become increasingly important for identifying novel disease mechanisms and predicting drug efficacy [7,8]. For example, one recent study proposed a symptom network approach to improve the understanding of mental disorders; in this approach, disorders are conceptualized as complex dynamic systems of interacting symptoms [9]. According to a related study on mental disorders [10], a strongly connected symptom network may be associated with less positive prospects. If this situation is held true for pediatric cough, then we should expect symptoms to be strongly connected within the pediatric cough groups that have worse efficacy.

Here, we investigate a symptom network of pediatric cough and evaluate its association with clinical effectiveness for treatment. In this study, similar to the work on mental disorders [10], overall network connectivity was compared using the recently developed Network Comparison Test (NCT) [11]. Local connectivity of individual symptoms in the network was compared using four centrality measures (node betweenness, closeness, strength, and eigenvector centrality) [12].

Materials and methods

Study sample

The data set was selected from the electronic medical records of a TCM physician (co-author of this work) from November 2006 to June 2014 in the Hubei Provincial Hospital of Traditional Chinese Medicine and the Guangzhou Clifford Hospital, with permission. A total of 496 patients with 1640 cases were screened for the diagnosis of pediatric cough.

Using the platform for handling medical records [13] and checking the original medical records, we selected 254 patients, 384 cases (patient-visits) for this study, on the basis of the following inclusion criteria: (1) the diagnosis was cough, (2) the case had a therapeutic effect, and (3) Chinese herbal treatments were used in every case. The exclusion criteria were (1) the case only had one medical record and (2) these cases, diagnosed cough, were actually cold [14], asthma [15], and pneumonia [16]. To evaluate the effectiveness of different cases, we considered the change in symptoms between the sequential consultations as the main indicator. For example, cough was the main symptom of pediatric cough. If "cough reduction," "occasional cough," or "no cough" appeared in the subsequent visit, it was considered effective. By contrast, "cough aggravation" or "no change of cough occurred" indicated ineffective. The evaluation of efficacy was divided into four categories, namely, recovery, improvement, no change, and deterioration. Recovery and improvement were categorized as valid, whereas no change and deterioration were invalid. This study was a retrospective case research; thus, the therapeutic effect was assessed on the basis of the symptoms change. After evaluation, we obtained 384 cases (patient-visits) that met the above-mentioned criteria; 344 cases were considered valid, and the remaining cases were considered invalid. The number of patients and cases before and after evaluation is shown in Table 1, and the interval time between one patient-visit and its subsequent patient-visit is shown in Table 2.

Table 1 Number of patients and cases before and after evaluation[a]

Number of total patients	496
Number of total cases	1640
Number of patients with efficacy evaluation	254
Number of cases with efficacy evaluation	384

[a] In the data set, one patient may be associated with one or more cases; patient ID and case ID were used to identify the link between patients and cases, respectively.

Table 2 Distribution of interval time between two consecutive cases

Interval time	Cases
1–7 days	336
8–14 days	44
>14 days	4

In our study, if one symptom occurred in a case, then the score of this symptom is 1, and the opposite is 0. We used the Pearson's correlation coefficient to measure the correlation between two symptoms. The coefficient is the covariance of the two variables divided by the product of their standard deviations. The formula of the correlation between symptom X and symptom Y is

$$\rho(X,Y) = \frac{cov(X,Y)}{\sigma_X \sigma_Y}, \quad (1)$$

where $cov(X,Y)$ is the covariance, σ_X is the standard deviation of X, and σ_Y is the standard deviation of Y. The Pearson's correlation coefficient ranged from -1 to 1 [17].

However, σ_X was 0 if symptom X occurred in all cases or not in a group, which indicated that symptom X is a constant. For example, if all cases had the symptom of cough, then no correlation was observed between cough and other symptoms. Thus, we removed those symptoms from the follow-up analysis. A total of 52 symptoms

remained. Table 3 lists the abbreviations and full names of the 52 symptoms. Groups A and B represent the invalid and valid groups, respectively. Supplementary Tables S1 and S2 show the deleted symptoms in both groups and full names of the deleted symptoms, respectively.

Statistical analysis

General differences

The Wilcoxon rank sum test, a non-parametric test that compares two paired groups [18], was used to test differences in each symptom between groups A and group B. The significance level for all analysis was 0.05. Statistical analysis was performed using R-package version 3.4.1 [12].

Network construction

The network structures were investigated separately for groups A and B using Pearson's correlations among symptoms. In the network, the nodes represent symptoms and the edges represent the correlation between symptoms. The weight of edges indicates the absolute value of correlation between symptoms. The correlation networks were performed using Qgraph, which was implemented in R-package Qgraph [19].

Differences in overall connectivity

We used four overall connectivity measures, namely, global strength, average shortest path length, diameter, and density, to analyze the differences between the two symptom networks.

The global strength of the network is defined as the weighted sum of the absolute connections [20]. The formula of global strength *GS* is

$$GS = \sum\nolimits_{i \neq j} w_{i,j}, \tag{2}$$

where $w_{i,j}$ is the weight (the absolute value) between symptoms i and j.

The atverage shortest path length is the average number of steps along the shortest paths for all possible pairs of symptoms [21]. The formula of average shortest path length *ASPL* is

$$ASPL = \frac{1}{n \cdot (n-1)} \cdot \sum\nolimits_{i \neq j} d_{i,j}, \tag{3}$$

where n is the size of the graph, that is, the total number of symptoms in the network; and $d_{i,j}$ denotes the shortest distance between symptoms i and j.

Diameter is the maximum shortest path length in the network, which is the greatest distance between any two symptoms [22]. The formula of diameter *DIA* is

$$DIA = \max_{i \neq j} d_{i,j}. \tag{4}$$

Table 3 Full names of the 52 symptoms

Symptom	Abbreviation	Symptom	Abbreviation	Symptom	Abbreviation
White-coated tongue	wct	Pharyngalgia	phg	Prickly tongue	ptt
Pharyngeal red	phr	Yellow coated tongue	yct	Abdominal pain	abp
Thin tongue coating	thc	Constipation	con	Dark red throat	drt
Fingerprint in life pass	flp	Fingerprint in wind pass	fiw	Fingerprint in qi pass	fqp
Moderate pulse	mop	Loose stool	lst	Rapid pulse	rpp
Anorexia	ano	Sneezing	snz	Yellow sputum	ysp
Red tongue	rtg	Pulmonary rales	pmr	Fine fingerprints	fif
Thready pulse	thp	Nasal secretions	nas	White sputum	wsp
Expectoration	exp	Nasal mucus	nam	Vomiting	vom
Slippery pulse	slp	Thin tongue coating	ttc	Nasal discharge	nsd
Antiadoncus	ant	Wheeze	whz	Purulent snot	psn
Nasal obstruction	nao	Sleep disturbed	sld	Postnasal drip	pod
Pink tongue	pkt	Throat secretions	ths	Barking cough	bcg
Fever	fev	Poor complexion	pcp	Deep red tongue	dpg
Conjunctival congestion	cjc	Purple red fingerprint	prf	Lavender fingerprints	lvf
Pulmonary breath sounds rough	pbs	Inflamed lymph follicles of the throat	ilt	Swollen lymph follicles of the throat	slft
Unconspicuous fingerprint	ucf	Night crying	ncr		
Thick coated tongue	tct	Erythra	eth		

The density of a network is the ratio of the numbers of edges and possible edges [22]. The formula of density *DEN* is

$$DEN = \frac{m}{n \cdot (n-1)}, \quad (5)$$

where m is the total number of edges and n is the total number of nodes in the network.

Statistical assessment of the difference in overall connectivity between networks of both groups was performed using NCT, a two-tailed permutation test [23], in which the differences of the four measures between groups A and B were calculated 100 000 times for randomly regrouped individuals. This performance resulted in a distribution under the null hypothesis assuming that both groups were equal, which could be used to test the difference between two groups. The difference was considered significant at a threshold of 0.05.

Differences in local connectivity

We used four best local centrality measures, namely, node strength, closeness, betweenness, and eigenvector centrality, to reveal which symptoms are important in the corresponding symptom network.

Node strength is a direct metric to characterize the centrality in a network. The method of calculating strength is to sum up the edge weights of the adjacent edge for each node [20]. When the strength is large, the degree centrality of this node is high, which indicates the node is more important than other nodes in the network. Here, the formula for the strength of symptom i is

$$S_i = \sum\nolimits_j w_{i,j}. \quad (6)$$

Closeness centrality measures the number of steps required to access every other node from a given node. The closeness centrality of a node is defined by the inverse an average length of the shortest path from all the other nodes in the network. Thus, the more central a node is, the closer it is to all other nodes [24]. The formula for the closeness of symptom i is

$$C_i = \frac{1}{\sum\nolimits_j d_{i,j}}. \quad (7)$$

Betweenness centrality quantifies the number of times a node acts as a bridge along the shortest path between two other nodes. A node with a high betweenness centrality will have strong control over the network [22]. The formula for the betweenness of symptom i is

$$B_i = \sum\nolimits_{i \neq j \neq k} \frac{\sigma_{jk}(i)}{\sigma_{jk}}, \quad (8)$$

where σ_{jk} is total number of shortest paths from symptom j to symptom k and $\sigma_{jk}(i)$ is the number of those paths that passes through symptom i.

However, the importance of a node also depends on the importance of its neighbors [24,25]. Eigenvector centrality measures the degree to which the node is connected to other central nodes; they correspond to the values of the first eigenvector of the graph adjacency matrix. This metric is proportional to the sum of the centrality of nodes connected to the focal node [26]. Let $M=(m_{i,j})$ be the graph adjacency matrix, i.e., $m_{i,j}$ is the absolute connection between symptom i and symptom j. The related eigenvector equation about matrix M is $ME=\lambda E$, where λ is the unique largest eigenvalue and E is the corresponding eigenvector. The i^{th} component of the eigenvector E then gives the eigenvector centrality score of the symptom i in the symptom network.

Quantifying importance of symptoms

To quantify the importance of symptoms in two symptom networks, we calculated the effect size for differences in mean local centrality of symptoms between groups A and B. Symptoms with the highest effect size were considered the most distinctive. Here, data of groups A and B were resampled 1000 times with the bootstrap method [27], which resulted in the distribution of all symptom local centrality measures in both groups. Cohen's d [27] was used to calculate the effect size of each symptom. Given that we considered node strength, closeness, betweenness, and eigenvector, the effect size of each symptom was the average of effect sizes in the four measures.

Results

General differences

The age and gender distributions of the 384 cases in groups A and B are shown in Tables 4 and 5, respectively. We performed a permutation test to analyze the differences in age and gender, and the significance level was 0.05. The P value of age was 0.44, and the P value of gender was 0.97; no significant difference was observed in age and gender.

Statistical analysis showed that the mean score value of 37 symptoms in group A was higher than that in group B (Table 6). A total of 50 symptoms (96.15%) had a P value > 0.05, which indicated that the single symptom could not cause a significant difference in effectiveness. Only two symptoms, namely, thready pulse (thp) and pulmonary rales (pmr), had P values of less than 0.05.

Differences in overall connectivity

From the two symptom correlation networks, we found

Table 4 Age distribution of groups A and B

Age group	Group A (cases)	Group B (cases)
Newborn baby (1 day<age⩽28 days)	0	2
Infancy (28 days<age⩽1 year)	2	37
Toddler period (1 year<age⩽3 years)	17	94
Pre-school age (3 years<age⩽7 years)	17	176
School age (7 years<age⩽13 years)	4	35

Table 5 Gender distribution of groups A and B

Gender	Group A (cases)	Group B (cases)
Boys	25	209
Girls	15	135

that the network of group A was more strongly connected than that of group B (Fig. 1). We counted the number of positive and negative correlation coefficients in two networks; the significance level was less than 0.05 (Table 7). We also selected the 20 highest absolute values of positive and negative correlations of the two networks (Table 8). The positive correlation value between symptoms of the invalid group was higher than that of the valid group. A large absolute value indicates a strong correlation. If the positive correlation is large, then the two symptoms will occur frequently. Otherwise, the occurrence will be less frequent. In the invalid group, seven pairs of symptoms had weights of 1. They were as follows: swollen lymph follicles of the throat (slft) and deep red tongue (dpg), throat secretions (ths) and barking cough (bcg), conjunctival congestion (cjc) and pharyngalgia (phg), yellow sputum (ysp) and fingerprint in life pass (flp), sleep disturbed (sld) and night crying (ncr), throat secretions (ths) and fine fingerprints (fif), and barking cough (bcg) and fine fingerprints (fif). However, the positive correlation values of group B were all less than 1.

As shown in Fig. 2, the average shortest path length, density, diameter, and global strength of group A were all higher than those of group B (Fig. 2). A significant difference in density, diameter, and global strength ($P < 0.05$) was found between groups A and B (Table 9).

Differences in local connectivity

To investigate differences in local connectivity, we compared the networks of groups A and B on the basis of the four centrality measures (Fig. 3).

Similar patterns were found when node strength was analyzed (Fig. 3). By contrast, barking cough (bcg), fine fingerprints (fif), fingerprint in wind pass (fiw), loose stool (lst), nasal mucus (nam), thick coated tongue (tct), throat secretions (ths), and white-coated tongue (wct) had higher values in the invalid cases' network. In terms of closeness (Fig. 3), all symptoms had a higher value in the invalid cases' network. However, the closeness of the invalid cases' network was close to 0. Regarding betweenness (Fig. 3), the value in the invalid cases' network was high in the following symptoms: expectoration (exp), fingerprint in wind pass (fiw), lavender fingerprints (lvf), nasal mucus (nam), thick coated tongue (tct), and white-coated tongue (wct). Similar to closeness, the betweenness in the valid cases' network was also close to 0. The eigenvector centrality had a different pattern in two networks (Fig. 3). The symptoms barking cough (bcg), fine fingerprints (fif), nasal mucus (nam), pink tongue (pkt), and throat secretions (ths) had a high value in the invalid cases' network. In the valid cases' network, symptoms that had a high value were fingerprint in wind pass (fiw), lavender fingerprints (lvf), slippery pulse (slp), and thready pulse (thp).

From all four centrality measures, two symptoms had high values of effect size, namely, expectoration (exp) and constipation (con), with effect sizes of 3.21 and 3.03, respectively (Table 10). Nasal discharge (nsd, effect size = 2.88), pulmonary breath sounds rough (pbs, effect size = 2.81), anorexia (ano, effect size = 2.61), antiadoncus (ant, effect size = 2.51), pharyngeal red (phr, effect size = 2.30), nasal obstruction (nao, effect size = 2.20), and sneezing (snz, effect size = 2.03) also had high effect size values (Table 10).

Discussion

TCM has a long history of viewing an individual or patient as a system with different statuses and has accumulated abundant clinical experience, thereby forming a comprehensive and unique medical system. Compared with western medicine, TCM usually focuses on functional clinical phenotype investigation, which constructs the evidence chain of TCM diagnosis and treatment [28].

The physiologic characteristics of children include delicate and immature zang-fu organs, insufficient physique and qi, vigorous activity, and rapid growth and development. The main pathology that children manifest is that they are easily attacked by diseases. When they are sick, their condition tends to change quickly and becomes serious with improper treatment. However, children also have pure and clear zang qi that helps them to make a quick recovery. Therefore, conducting proper interventions on symptoms immediately is important [6].

In our study, we found two symptoms (pmr and thp) that were significantly different in different efficacy groups. Rhonchi is the sound produced by turbulence that occurs during inhalation or exhalation of the airflow due to the narrow or partial obstruction of the trachea or bronchi. When the airflow passes through the bronchus that contains thin secretions (exudate, mucus, pus, and

Table 6 General difference analysis of symptom of groups A and B

Symptom	Mean		SD		Statistic	*P* value
	Group A	Group B	Group A	Group B		
phr	0.85	0.81	0.36	0.40	7188	0.50
wct	0.78	0.79	0.42	0.41	6792	0.85
nsd	0.65	0.61	0.48	0.49	7172	0.60
ahc	0.58	0.52	0.50	0.50	7256	0.51
ano	0.50	0.48	0.51	0.50	7000	0.84
thp	0.23	0.39	0.42	0.49	5748	0.04
rtg	0.43	0.38	0.50	0.49	7204	0.56
mop	0.43	0.37	0.50	0.48	7244	0.51
exp	0.43	0.30	0.50	0.46	7724	0.11
slp	0.15	0.29	0.36	0.46	5892	0.06
pkt	0.15	0.22	0.36	0.41	6412	0.32
nao	0.13	0.21	0.33	0.41	6300	0.21
pmr	0.05	0.20	0.22	0.40	5824	0.02
lvf	0.30	0.19	0.46	0.40	7604	0.12
fiw	0.28	0.19	0.45	0.39	7452	0.21
tct	0.13	0.19	0.33	0.39	6420	0.30
con	0.30	0.18	0.46	0.38	7704	0.07
ant	0.18	0.17	0.38	0.38	6884	0.99
pbs	0.15	0.16	0.36	0.37	6792	0.84
fev	0.10	0.16	0.30	0.37	6468	0.32
nam	0.15	0.13	0.36	0.34	7012	0.74
yct	0.10	0.12	0.30	0.32	6748	0.72
snz	0.08	0.10	0.27	0.30	6716	0.63
Lst	0.05	0.09	0.22	0.29	6584	0.37
ucf	0.05	0.09	0.22	0.29	6604	0.39
psn	0.05	0.06	0.22	0.24	6804	0.78
whz	0.05	0.06	0.22	0.23	6824	0.84
prf	0.13	0.05	0.33	0.22	7400	0.05
nas	0.08	0.05	0.27	0.22	7056	0.49
ttc	0.08	0.04	0.27	0.20	7116	0.32
ths	0.05	0.03	0.22	0.18	6984	0.63
cjc	0.03	0.03	0.16	0.17	6852	0.89
pcp	0.05	0.03	0.22	0.17	7024	0.47
drt	0.05	0.02	0.22	0.15	7064	0.32
sld	0.03	0.02	0.16	0.15	6892	0.95
eth	0.03	0.02	0.16	0.15	6892	0.95
ysp	0.03	0.02	0.16	0.14	6912	0.85
rpp	0.03	0.02	0.16	0.14	6912	0.85
phg	0.03	0.02	0.16	0.14	6912	0.85
ptt	0.03	0.02	0.16	0.13	6932	0.74
vom	0.03	0.02	0.16	0.13	6932	0.74
fqp	0.05	0.02	0.22	0.13	7104	0.17
abp	0.03	0.02	0.16	0.13	6932	0.74
ilt	0.03	0.01	0.16	0.12	6952	0.62
slft	0.03	0.01	0.16	0.11	6972	0.48
dpg	0.03	0.01	0.16	0.11	6972	0.48
bcg	0.05	0.01	0.22	0.11	7144	0.06
wsp	0.03	0.01	0.16	0.11	6972	0.48
fif	0.05	0.01	0.22	0.11	7144	0.06
pod	0.03	0.01	0.16	0.08	7012	0.19
ncr	0.03	0.01	0.16	0.08	7012	0.19
flp	0.03	0.00	0.16	0.05	7032	0.07

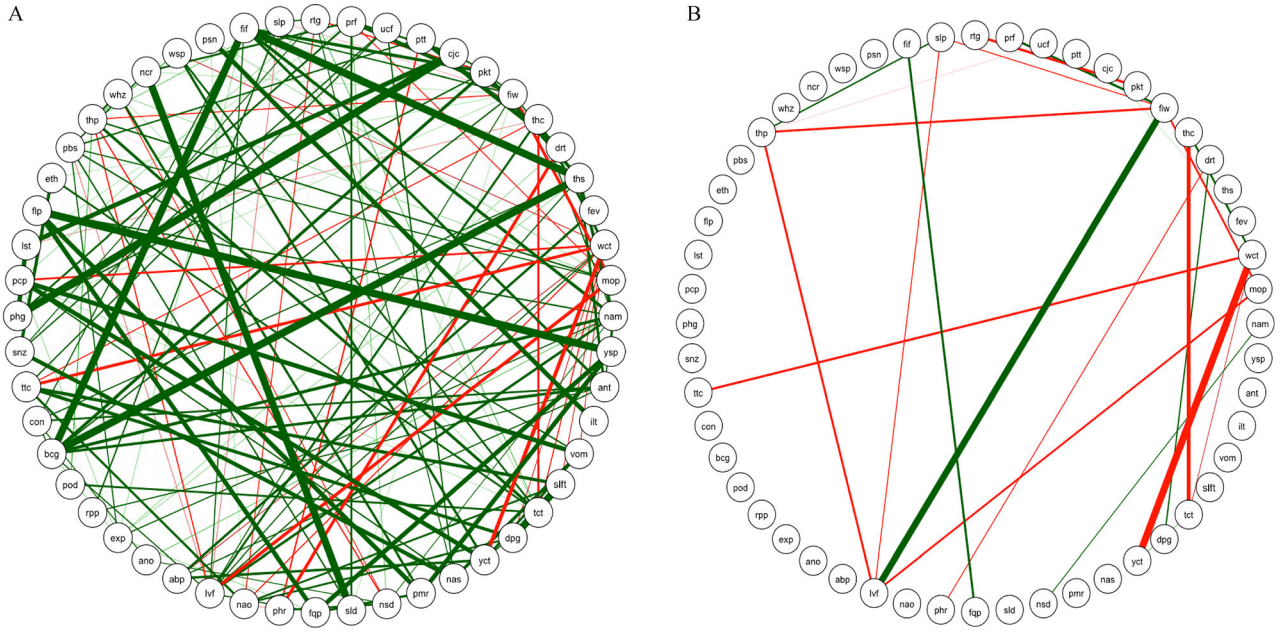

Fig. 1 Symptom network structure of groups A and B. (A) Symptom correlation network of group A. (B) Symptom correlation network of group B. The symptom is represented as a node, and the Pearson's correlation coefficient between two symptoms is represented as an edge. The green edges in (A) represent positive correlations, and the red edges represent negative correlations. The thick edges in (B) represent strong correlations, and the red edges represent negative correlations (positive or negative). Only edges with correlation coefficients larger than 0.24 are shown in the figure.

Table 7 Positive/negative correlation coefficient distribution of groups A and B

	Group A (cases)	Group B (cases)
Positive	395	931
Negative	515	811

blood), the sound that occurs when the liquid forms blisters and ruptures immediately is known as "moist crackles." The two pulmonary rales reflect inflammation of trachea or bronchi seriously, which may result in significant differences between groups A and B. Thready pulse indicates physiological characteristics of insufficient physique, qi, and blood, which may be the reason for significant differences between the two groups. However, most symptoms in both groups did not show significant differences in effectiveness, which indicates that not a single symptom but the symptom interactions have an impact on efficacy [29].

To our knowledge, this study is the first to use the network approach for identifying the symptom interactions as regards clinical effectiveness in TCM. Here, we find that the symptom network of pediatric cough patients with poor treatment effect (group A) is denser than that of patients with effective treatment (group B). In our study, the valid group with a sparse symptom network indicates weak

Table 8 Positive correlation and negative correlation values of the symptom network diagram

Invalid group			Valid group		
Symptom	Symptom	Weight	Symptom	Symptom	Weight
slft	dpg	1.00	fiw	lvf	0.67
ths	bcg	1.00	prf	lvf	0.40
cjc	phg	1.00	fqp	fif	0.40
ysp	flp	1.00	thc	wct	0.38
sld	ncr	1.00	thp	slp	0.35
ths	fif	1.00	drt	dpg	0.34
bcg	fif	1.00	nam	nsd	0.31
ptt	drt	0.70	tct	yct	0.28
ysp	fqp	0.70	cjc	fev	0.26
fqp	flp	0.70	drt	pod	0.24
nsd	thp	−0.36	fiw	slp	−0.31
rtg	pkt	−0.36	lvf	slp	−0.32
ptt	phr	−0.38	fiw	mop	−0.38
wct	pcp	−0.43	mop	lvf	−0.38
thc	tct	−0.44	fiw	thp	−0.39
wct	ttc	−0.53	lvf	thp	−0.39
fiw	mop	−0.53	wct	ttc	−0.40
drt	phr	−0.55	rtg	pkt	−0.41
mop	lvf	−0.56	thc	tct	−0.51
wct	yct	−0.62	wct	yct	−0.71

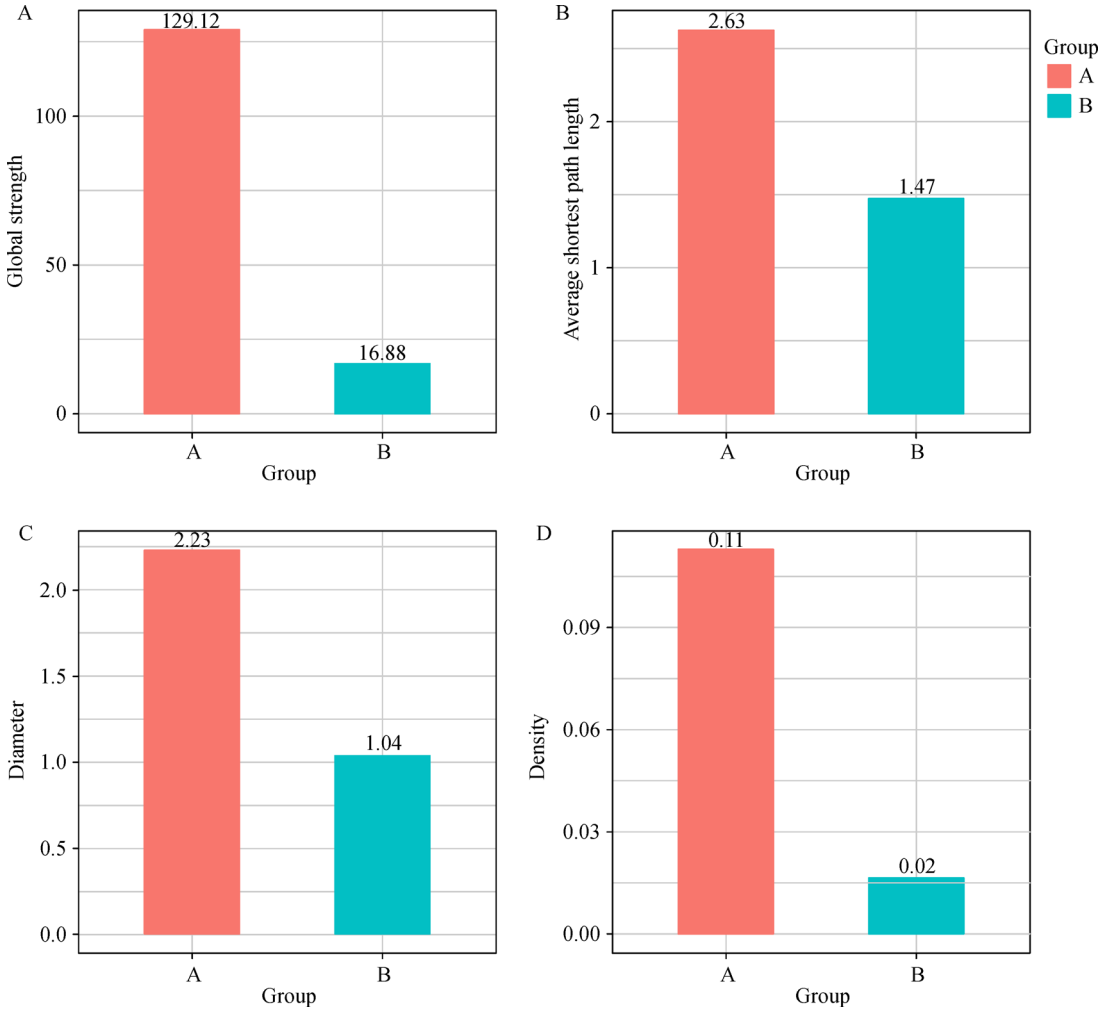

Fig. 2 Overall connectivity measures of groups A and B. The color of columns shows different groups. (A) Global strength of groups A and B. (B) Average shortest path length of groups A and B. (C) Diameter of groups A and B. (D) Density of groups A and B.

Table 9 Results of permutation test with networks

Network metric	*P* value
Global strength	<0.05
Average shortest path length	>0.05
Diameter	<0.05
Density	<0.05

symptom interaction; that is, symptoms in the valid group appear singly. Therefore, the symptom interaction of the valid group is lower than that of the invalid group, which may be an important cause for a good or poor curative effect.

Furthermore, we find that the symptoms, namely, expectoration (exp), constipation (con), nasal discharge (nsd), pulmonary breath sounds rough (pbs), anorexia (ano), antiadoncus (ant), pharyngeal red (phr), nasal obstruction (ano), and sneezing (snz), identified by local centrality measures, are more significant in group A than in B. All these symptoms with high effect sizes also represent the diversity of pediatric cough, and they also tend to be accompanied with various symptoms. This finding indicates that the complexity of the clinical pathogenesis may be the reason for the poor treatment effect. At the same time, these symptoms are particularly plausible for intervention. In the clinical process, those symptoms are accompanied by symptoms of pediatric cough, and doctors

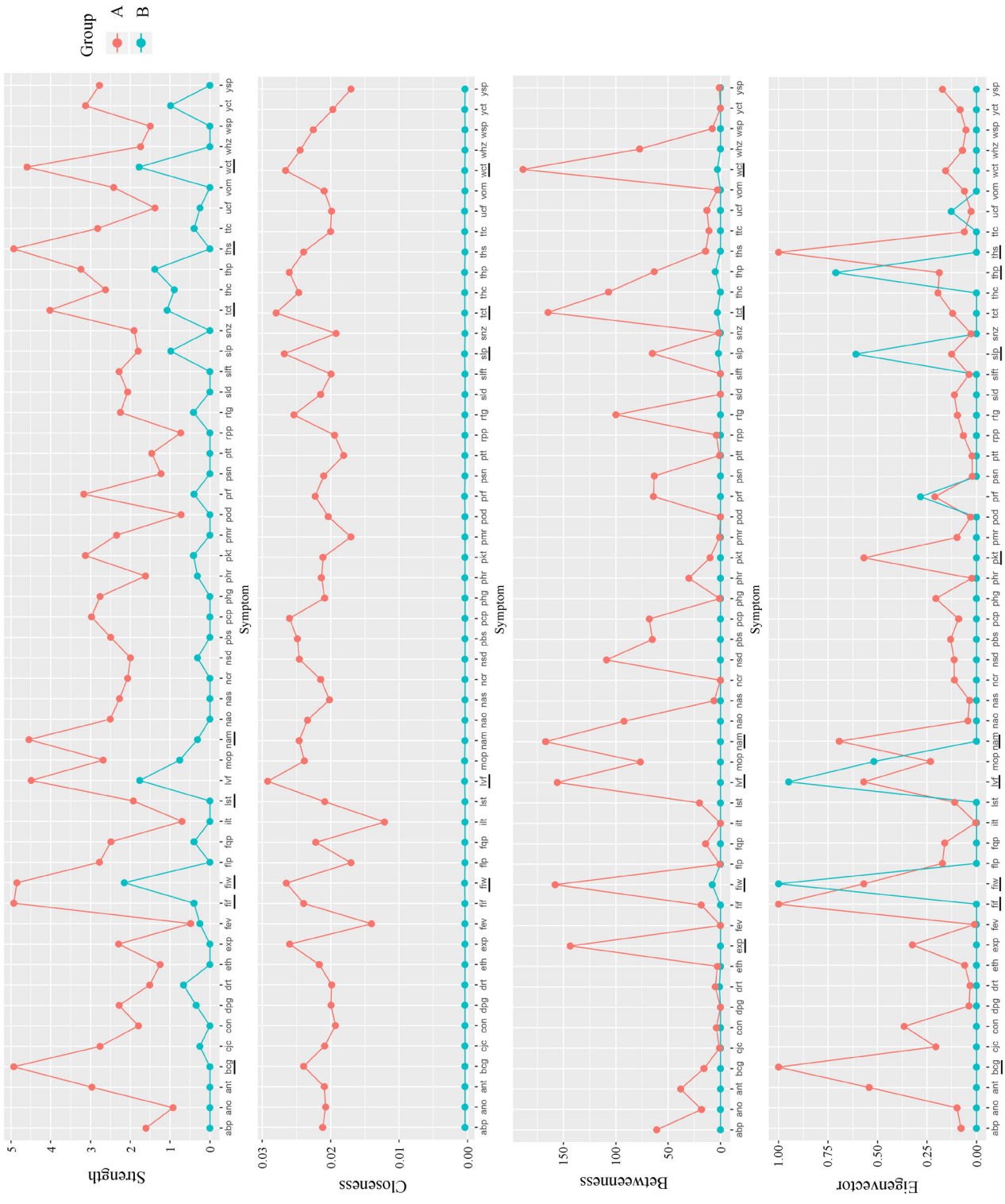

Fig. 3 Four node centrality measures of groups A and B: strength, closeness, betweenness, and eigenvector.

Table 10 Effect sizes for differences in mean centrality between groups A and B[a]

Symptom	Effect size	Symptom	Effect size	Symptom	Effect size
exp	3.21	ths	1.79	ysp	0.97
con	3.03	fev	1.70	vom	0.91
nsd	2.88	pcp	1.60	sld	0.90
pbs	2.81	whz	1.47	ncr	0.88
ano	2.61	psn	1.38	cjc	0.86
ant	2.51	abp	1.16	slft	0.86
phr	2.30	wsp	1.10	ilt	0.85
nao	2.20	drt	1.05	pod	0.84
snz	2.03	lst	1.04	phg	0.80
nas	1.97	eth	1.00		

[a] Pictures of tongue and pulse condition in this table were excluded.

often intervene in them. Pulmonary breath sounding rough is a main point in the diagnosis of pediatric cough [6]. For instance, Professor Wang often uses common drug combinations to treat constipation and anorexia [30]. Professor Nie estimates the nature of pediatric cough due to exopathy on the basis of the condition of laryngopharynx. In addition, he indicates that pharyngeal red represents that the nature of the cough is heat, which should be interfered [31]. Therefore, the information on local connectivity may guide clinical therapy. However, additional research is needed to confirm this hypothesis. For example, which centrality measure is clinically most relevant in identifying the importance of symptoms has yet to be established. Although a central symptom is likely to have an influence on other nodes, it may be an efficient target for intervention if associations with other symptoms are directed outward or are at least bidirectional [32].

The key advantages and strengths of this study are as follows. Compared with the previous studies, we used the method of analyzing the network structure to investigate the relationship between symptoms and efficacy on pediatric cough. Our clinical data curated from Professor Ni and the previous studies [33] showed that Professor Ni used the same therapeutic process to treat pediatric cough, which makes our work feasible by evaluating the effectiveness only from the clinical feature perspective. In addition, we performed statistical comparison based on NCT and effect size for differences that made our results reliable. However, our study has several potential limitations. First, TCM is environment sensitive, and our data are imperfect because of lacking fine details on their population distribution. In addition, this study was conducted on the basis of a relatively small volume of the retrospective data derived from a single TCM physician. Furthermore, no reliable method is available to determine what symptoms in both networks directly lead to good or poor outcomes, which has significant implications for TCM clinical practice. In the future work, we will incorporate additional cases from different physicians or attempt a well-designed prospective study to validate the findings. We also intend to develop a reasonable method to determine what symptoms in both networks directly lead to good or poor outcomes.

Conclusions

This study reports that symptom networks of patients with pediatric cough are related to the effectiveness of treatment: a dense baseline network of symptoms is associated with great difficulty in treatment. Additional symptom interaction may be an important reason for the difficulty in treating pediatric cough. This proof-of-principle concept on symptom network is a promising line of research and can provide feasible approaches for the TCM diagnosis and treatment of other diseases.

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Compliance with ethics guidelines

Mengxue Huang, Jingjing Wang, Runshun Zhang, Zhuying Ni, Xiaoying Liu, Wenwen Liu, Weilian Kong, Yao Chen, Tiantian Huang, Guihua Li, Dan Wei, Jianzhong Liu, and Xuezhong Zhou declare that they have no conflict of interest. No ethics approval was required because no experiments on humans or animals were carried out.

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